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CONTENTS

NEW SERIES, VOLUME 2, NUMBER 5, JANUARY 1933

Congenital Stenosis (Coarctation), Atresia, and Interruption of the Aortic Arch. (A Study of Twenty-eight Cases.) By William Evans. With Plates 1 to 3 1

The Therapeutic Use of Drugs of the Digitalis Group. By Elsie Porter. With Plates 4 to 8 33

Hepato-Lienography by the Aid of Thorotrast—Its Uses and Dangers. By P. H. Whitaker, T. B. Davie, and F. Murgatroyd. With Plates 9 to 12 49

Linitis Plastica: A Study of Ten Cases. By C. P. Howard. With Plates 13 and 14 59

The Erythrocyte Sedimentation Test. A Clinical and Experimental Study. By A. C. Rees Walton. With Plate 15 79

Critical Review: Hypoglycaemia. By G. M. Wauchope 117

NUMBER 6, APRIL 1933

Uveo-parotid Tuberculosis (Febris Uveo-parotidea of Heerfordt). By Hugh G. Garland and J. G. Thomson. With Plates 16 to 18 157

The Value of Artificial Pneumothorax in Pulmonary Tuberculosis. By Cedric Shaw 179

A Comparison between the Bendien Chemical Test and Sedimentation-rate Test in the Prognosis of Tuberculosis. By Joseph Fine and D. Melville Dunlop 201

Pathological Changes in the Carotid Sinus and their Relation to Hypertension. By C. A. Keele 213

The Electrocardiogram in Syphilis. An Examination of 232 Cases of Syphilis and 156 Controls. By E. Noble Chamberlain and J. H. Follows. With Plates 19 to 22 221

Renal Dwarfism. A Report of 20 Cases with Special Reference to its Association with certain Dilatations of the Urinary Tract. By Arthur Ellis and Horace Evans. With Plates 23 to 27 231

Precipitin Reactions in the Blood of Rheumatic Patients following Acute Throat Infections. By Bernard Schlesinger and A. Gordon Signy . 255

Diabetic Lipaemia. The Role of the Fats in Diabetes Mellitus, with a Description of the Haemolipokrit Method for the Estimation of Fat in the Blood-serum. By Douglas H. Collins 267

NUMBER 7, JULY 1933

Diseases Associated with Pernicious Anaemia. (In a Study of 370 Cases.) By John F. Wilkinson 281

The Comparative Value of Drugs Used in the Continuous Treatment of Angina Pectoris. By William Evans and Clifford Hoyle 311

Two Cases of 'Fatty Diarrhoea', with Special Reference to Nitrogen Metabolism. By A. Greig Anderson and Alexander Lyall. With Plates 28 and 29 339

Diabetes Mellitus and Pregnancy. A Clinical and Analytical Study. (With Special Observations upon Thirty-three Cases). By Eric Skipper . . 353

The Effect of Yeast and Wheat Embryo in Anaemias. I. Marmite, Yestamin, and Bemax in Megalocytic and Nutritional Hypochromic Anaemias. By Charles C. Ungley 381

Xanthomatosis generalisata ossium. By I. Snapper and Ch. Parisel. With Plates 30 to 33 407

Acid-base Equilibrium of Blood in Epilepsy. By Francis Leo McLaughlin and Richard Henry Hurst 419

Critical Review: Achlorhydria. By T. H. Oliver and John F. Wilkinson . 431

NUMBER 8, OCTOBER 1933

The Hypertensive Cerebral Attack. By Douglas McAlpine 463

The Action of Atropine in Complete Heart-block. By A. Rae Gilchrist. With Plates 34 and 35 483

The Action of Adrenalin in Complete Heart-block. By A. Rae Gilchrist. With Plates 36 to 38 499

Oedema in Nephritis. By J. Basil Rennie 521

Calcification of the Kidneys in Pyloric Stenosis. By A. M. Cooke. With Plate 39 539

Pituitary Secretion in High Blood-pressure. By Clifford Hoyle. With Plates 40 to 44 549

The Diagnosis of Anaemia with Special Reference to Cell Volume and Blood-iron Estimation. By Harold W. Fullerton, Alexander Lyall, and L. S. P. Davidson 561

Proceedings of the Association of Physicians of Great Britain and Ireland. Twenty-seventh Annual General Meeting 583

ERRATUM

Page 157, the contributor's name should be spelt J. G. THOMSON

INDEX OF CONTRIBUTORS

ANDERSON, A. G. Two Cases of 'Fatty Diarrhoea', with Special Reference to Nitrogen Metabolism. With Plates 28 and 29 339

CHAMBERLAIN, E. N. The Electrocardiogram in Syphilis. An Examination of 232 Cases of Syphilis and 156 Controls. With Plates 19 to 22 . 221

COLLINS, D. H. Diabetic Lipaemia. The Role of the Fats in Diabetes Mellitus, with a Description of the Haemolipokrit Method for the Estimation of Fat in the Blood-serum 267

COOKE, A. M. Calcification of the Kidneys in Pyloric Stenosis. With Plate 39 539

DAVIDSON, L. S. P. The Diagnosis of Anaemia with Special Reference to Cell Volume and Blood-iron Estimation 561

DAVIE, T. B. Hepato-Lienography by the Aid of Thorotrast—Its Uses and Dangers. With Plates 9 to 12 49

DUNLOP, D. M. A Comparison between the Bendien Chemical Test and Sedimentation-rate Test in the Prognosis of Tuberculosis . . . 201

ELLIS, A. Renal Dwarfism. A Report of 20 Cases with Special Reference to its Association with certain Dilatations of the Urinary Tract. With Plates 23 to 27 231

EVANS, H. Renal Dwarfism. A Report of 20 Cases with Special Reference to its Association with certain Dilatations of the Urinary Tract. With Plates 23 to 27 231

EVANS, W. Congenital Stenosis (Coarctation), Atresia, and Interruption of the Aortic Arch. (A Study of 28 Cases.) With Plates 1 to 3 . . 1

———— The Comparative Value of Drugs Used in the Continuous Treatment of Angina Pectoris 311

FINE, J. A Comparison between the Bendien Chemical Test and Sedimentation-rate Test in the Prognosis of Tuberculosis 201

FOLLOWS, J. H. The Electrocardiogram in Syphilis. An Examination of 232 Cases of Syphilis and 156 Controls. With Plates 19 to 22 . . 221

FULLERTON, H. W. The Diagnosis of Anaemia with Special Reference to Cell Volume and Blood-iron Estimation 561

GARLAND, H. G. Uveo-parotid Tuberculosis (Febris Uveo-parotidea of Heerfordt). With Plates 16 to 18 157

GILCHRIST, A. R. The Action of Atropine in Complete Heart-block. With Plates 34 and 35 483

———— The Action of Adrenalin in Complete Heart-block. With Plates 36 to 38 499

HOWARD, C. P. Linitis Plastica: A Study of Ten Cases. With Plates 13 and 14 59

HOYLE, C. The Comparative Value of Drugs Used in the Continuous Treatment of Angina Pectoris. 311

———— Pituitary Secretion in High Blood-pressure. With Plates 40 to 44 549

HURST, R. H. Acid-base Equilibrium of Blood in Epilepsy 419

KEELE, C. A. Pathological Changes in the Carotid Sinus and their Relation to Hypertension 213

LYALL, A. Two Cases of 'Fatty Diarrhoea', with Special Reference to Nitrogen Metabolism. With Plates 28 and 29 339

———— The Diagnosis of Anaemia with Special Reference to Cell Volume and Blood-iron Estimation 561

MCALPINE, D. The Hypertensive Cerebral Attack 463

MCLAUGHLIN, F. L. Acid-base Equilibrium of Blood in Epilepsy. . . . 419

MURGATROYD, F. Hepato-Lienography by the Aid of Thorotrast—Its Uses and Dangers. With Plates 9 to 12 49

PORTER, E. The Therapeutic Use of Drugs of the Digitalis Group. With Plates 4 to 8 33

OLIVER, T. H. Critical Review: Achlorhydria 431

PARISEL, CH. Xanthomatosis generalisata ossium. With Plates 30 to 33 . 407

Proceedings of the Association of Physicians of Great Britain and Ireland. Twenty-seventh Annual General Meeting 583

RENNIE, J. B. Oedema in Nephritis 521

SCHLESINGER, B. Precipitin Reactions in the Blood of Rheumatic Patients following Acute Throat Infections 255

SHAW, C. The Value of Artificial Pneumothorax in Pulmonary Tuberculosis 179

SIGNY, A. G. Precipitin Reactions in the Blood of Rheumatic Patients following Acute Throat Infections 255

SKIPPER, E. Diabetes Mellitus and Pregnancy. A Clinical and Analytical Study. (With Special Observations upon Thirty-three Cases) . . 353

SNAPPER, I. Xanthomatosis generalisata ossium. With Plates 30 to 33 . 407

THOMSON, J. G. Uveo-parotid Tuberculosis (Febris Uveo-parotidea of Heerfordt). With Plates 16 to 18 157

UNGLEY, C. C. The Effect of Yeast and Wheat Embryo in Anaemias. I. Marmite, Yestamin, and Bemax in Megalocytic and Nutritional Hypochromic Anaemias 381

WALTON, A. C. R. The Erythrocyte Sedimentation Test. A Clinical and Experimental Study. With Plate 15 79

WAUCHOPE, G. M. Critical Review: Hypoglycaemia 117

WHITAKER, P. H. Hepato-Lienography by the Aid of Thorotrast—Its Uses and Dangers. With Plates 9 to 12 49

Wilkinson, J. F. Diseases Associated with Pernicious Anaemia. (In a Study of 370 Cases) 281

——————— Critical Review: Achlorhydria 431

INDEX

Achlorhydria, 431; in apparently normal individuals, 432; in children, 434; in disease, 435; aetiology of, 435; symptoms of, 437; effects of gastrectomy and gastro-enterostomy on the secretion of the stomach, 442; associated with diseases of the blood, 444; and subacute combined degeneration of the spinal cord, 449; diseases of the pancreas, 450; rheumatoid arthritis, 451; in allergic and skin diseases, 452; treatment of, 453.

Adrenalin, action of, in complete heart-block, 499; ventricular range after, 501; influence of size of dose on ventricular response, 505; nature of action on ventricular pacemaker, 507; response of the auricles, 508; relation of auricular to ventricular responses, 509; course of reaction to, 513; atypical response to, 514.

Anaemia, diagnosis of, with special reference to cell volume and blood-iron estimation, 561; method of blood-iron estimation, 562; results in normal individuals, 564; results in the anaemias, 565; idiopathic microcytic anaemia, 568; haemoglobin saturation index and iron saturation index, 570; miscellaneous blood diseases, 571; diffraction methods, 573.

Anaemia, pernicious, diseases associated with, 281; pulmonary diseases, 283; tuberculosis, 283; cardiovascular, 286; diabetes mellitus, 286; diseases of thyroid gland, 289; dermatoses, 291; urinary, 292; malignant disease, 292; syphilis, 296; gastro-intestinal ulceration, 298; chronic intestinal obstruction, 301; miscellaneous, 303.

Anaemia, pernicious, and dysphagia, 386.

Anaemia, pernicious, typical, without achlorhydria, 386.

Anaemias, effect of yeast and wheat embryo in, 381; nutritional hypochromic, 383; a typical pernicious anaemia without achlorhydria, including an unusual case of dysphagia with anaemia (pernicious), 386; Addisonian pernicious anaemia, 390.

Angina pectoris, comparative value of drugs used in continuous treatment of, 311.

Aorta, coarctation of, anatomical varieties of, 3.

Aortic arch, atresia of, 1; congenital stenosis of, 1; interruption of, 1.

Atresia of the aortic arch, 1.

Atresia, congenital, of proximal portion of aortic arch, 17.

Atropine, action of, in complete heart-block, 483; the response to, 487; ventricular range after, 489; auricular range after, 491; course of reaction to, 493.

Bendien chemical test and sedimentation-rate test, a comparison between, in the prognosis of tuberculosis, 201; technique of the Bendien chemical test adopted, 201; technique of the sedimentation test adopted, 203; reasons for parallelism and for deviations from parallelism between sedimentation rate and the Bendien test, 211.

Blood, acid-base equilibrium of, in epilepsy, 419.

Blood of rheumatic patients following acute throat infections, precipitin reactions in, 255.

Blood-iron estimation, 562.

Blood-pressure, high, pituitary secretion in, 549.

Blood-sugar level in hypoglycaemia, 119.

Calcification of the kidneys in pyloric stenosis, 539.

Cardiovascular diseases associated with pernicious anaemia, 286.

Carotid sinus, pathological changes in, and their relation to hypertension, 213.

Chronic intestinal obstruction associated with pernicious anaemia, 301.

Coarctation of the aorta, anatomical varieties of, 3.

Coarctation of the aortic arch, 1.

Dermatoses associated with pernicious anaemia, 291.

Diabetes mellitus and pregnancy, 353; maternal and foetal mortality, influence of insulin, 353; insulin and the fertility of the diabetic, 354; influence of pregnancy upon diabetes, 355; causes of foetal death in the diabetic, 361; significance of glycosurias of pregnancy, 365; diagnosis, 366; treatment, 368.
Diabetes mellitus associated with pernicious anaemia, 286.
Diabetes mellitus, role of fats in, 267.
Diabetic lipaemia, 267.
Diagnosis of anaemia with special reference to cell volume and blood-iron estimation, 561.
Diarrhoea, fatty, two cases of, with special reference to nitrogen metabolism, 339.
Digitalis, administration of, per rectum, 41.
Digitalis dosage, massive, by mouth, 33.
Digitalis group, drugs of the, therapeutic use of, 33.
Digitalis, site of action of, 42.
Drugs, comparative value of, used in continuous treatment of angina pectoris, 311.
Drugs of the digitalis group, therapeutic use of, 33.
Dwarfism, renal, 231.
Dysphagia with pernicious anaemia, 386.

Electrocardiogram in syphilis, 221.
Epilepsy, acid-base equilibrium of blood in, 419.
Erythrocyte sedimentation test, 79; study of experimental conditions, 80; personal technique, 82; normal sedimentation rate and its modifications in physiological states, 85; modifications of the sedimentation rate in pathological conditions and the application of the sedimentation test to different branches of medicine, 87; application of the sedimentation test to clinical medicine, 91.

Fats, role of, in diabetes mellitus, 267.
Febris uveo-parotidea of Heerfordt, 157.

Gastro-intestinal ulceration associated with pernicious anaemia, 298.

Haemolipokrit method, description of, for the estimation of fat in the blood-serum, 267.
Haemolipokrit pipette, description of, 270.
Heart-block, complete, action of atropine in, 483; action of adrenalin in, 499.
Heerfordt, febris uveo-parotidea of, 157.
Hepato-lienography by the aid of thorotrast, 49; technique and dosage, 51; clinical effects, 51; radiological findings, 52; pathological findings, 53.
Hypertension, the relation of pathological changes in the carotid sinus to, 213.
Hypertensive cerebral attack, 463; with signs of cerebral oedema, 467; without signs of cerebral oedema, 470; minor angiospastic cerebral symptoms, 475.
Hypoglycaemia, 117; blood-sugar level in, 119; symptomatology of, 121; pathogeny of, 126; morbid anatomy of, 129; insulin, a cause of, 139; diagnosis of, 147; prevention and treatment of, 150.

Insulin, influence of, on a pregnant diabetic, 354; and the fertility of a diabetic, 354: a cause of hypoglycaemia, 139.
Interruption of the aortic arch, 1; of aortic arch in distal position, 16.

Kidneys, calcification of, in pyloric stenosis, 539.

Linitis plastica, 59: aetiology of, 63; pathogenesis, 65; morbid anatomy of, 66; histology, 69; summary of the pathogenesis and pathology of, 69; symptoms of, 71; radiological examination in, 73; diagnosis of, 73; prognosis of, 74; treatment of, 75.
Lipaemia, diabetic, 267.

Malignant disease associated with pernicious anaemia, 292.
Mouth, massive digitalis dosage by, 33.

Nervous phenomena in uveo-parotid tuberculosis, 174.
Nephritis, oedema in, 521; relationship of serum protein to oedema in acute, 532.

Oedema in nephritis, 521; normal controls, 524; groups associated with, 525; relationship of serum protein to, 532.

Pituitary secretion in high blood-pressure, 549.

Pneumothorax, artificial, value of, in pulmonary tuberculosis, 179; comparison of the material of, with the Midhurst, 180; an attempt to assess the value of sanatorium treatment in conjunction with, 193.
Precipitin reactions in the blood of rheumatic patients following acute throat infections, 255; the precipitin test, 255; precipitin formation, 256; specificity of precipitin formation, 259; time relationship and strength of precipitin reaction, 259; effect of aspirin, 260; sedimentation rate, 260.
Pregnancy, influence of, upon diabetes, 355; significance of the glycosurias of, 365.
Pulmonary diseases associated with pernicious anaemia, 283.

Rectum, administration of digitalis per, 41.
Renal dwarfism, 231.
Rheumatic patients, blood of, following acute throat infections, precipitin reactions in, 255.

Stenosis, congenital, of the aortic arch, 1.
Stenosis, pyloric, calcification of kidneys in, 539.
Syphilis, the electrocardiogram in, 221; associated with pernicious anaemia, 296.

Thorotrast, hepato-lienography by aid of, 49; technique and dosage, 51; clinical effects, 51; radiological findings, 52; pathological findings, 53.
Thyroid gland, diseases of, associated with pernicious anaemia, 289.
Tuberculosis, the prognosis of, a comparison between the Bendien chemical test and sedimentation-rate test in, 201; associated with pernicious anaemia, 283.
Tuberculosis, pulmonary, value of artificial pneumothorax in, 179.
Tuberculosis, uveo-parotid, 157; clinical manifestations of, 157; nervous phenomena in, 174; prognosis of, 175; treatment of, 175.

Urinary diseases associated with pernicious anaemia, 292.
Uveo-parotid tuberculosis, 157; clinical manifestations of, 157; nervous phenomena in, 174; prognosis of, 175; treatment of, 175.

Xanthomatosis generalisata ossium, 407.

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CONGENITAL STENOSIS (COARCTATION), ATRESIA, AND INTERRUPTION OF THE AORTIC ARCH [1]

(A STUDY OF TWENTY-EIGHT CASES)

By WILLIAM EVANS

(From the Cardiac Department of the London Hospital)

With Plates 1 to 3

CONSTRICTION, actual occlusion, or absence of some portion of the aortic arch is not very uncommon as a finding at necropsy. Such anomalies are frequently associated with some other congenital deformity of the cardio-vascular system, but occasionally each may exist as the sole manifestation of faulty development. The deformity is compatible with life, and the severity of the stenosis appears to bear no constant relationship to duration of life; thus, actual atresia of the aorta may occasionally be discovered in the aged.

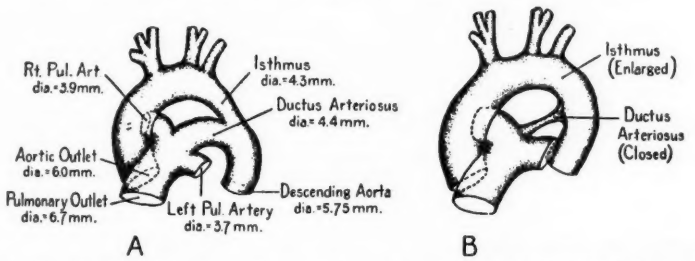

FIG. 1. Diagrams (after Patten) showing the characteristic post-natal change in the isthmic region of the aortic arch. (A) At full term. (B) Four months after birth.

This paper does not deal with the slight diminution in the calibre of that part of the vessel which forms the aortic isthmus (see Fig. 1). According to Théremin (1895) the gradual and slight narrowing found in this portion of the aortic arch, and situated between the left subclavian artery and the point where the ductus arteriosus enters, is a normal finding during the first three months of post-natal life in 80 per cent. of infants with healthy hearts. This paper discusses the more gross variety of the deformity which results in a pronounced degree of abrupt narrowing or even obliteration of the aortic lumen.

Incidence. Morgagni (1760) appears to have been the first observer to draw attention to this condition. When recording his findings at necropsy

[1] Received July 27, 1932.

in the case of a monk he referred to a condition of extreme constriction of the aorta occurring at a short distance from the heart. Evidence is now accumulating that, as clinicians are becoming familiar with the clinical syndrome presented by this congenital anomaly, its recognition in the living is a more frequent event. Even now it is probable that the lesion in its less pronounced form escapes detection at necropsy in a certain number of cases. Barié (1886) was able to review 89 published cases, and added an account of two which had come under his personal observation. Fawcett (1905), analysing the post-mortem records of Guy's Hospital from 1826 to 1902, found 18 cases of coarctation of the aorta in a routine post-mortem examination of 22,316 subjects. Abbott (1927) was able to study 237 cases collected from the literature. Reports on individual cases have since been added by many other observers.

The present series consists of 28 cases; 26 of these have been examined at necropsy. The remaining two cases are alive and in fair health. The 26 cases were found among 19,217 routine necropsies conducted at the Bernhard Baron Institute of Pathology, London Hospital. The condition therefore appears to have an incidence of 0·13 per cent. or approximately one in every thousand necropsies.

Age. From his analysis of the records of 20 cases with narrowing of the aorta, Burke (1901) found the average age was 23·8 years. King (1926), in a paper recording four instances of coarctation of the aorta in patients of 35, 40, 54, and 58 years of age, drew attention to the two critical periods through which such patients pass. Early infancy formed the first critical period, for during this time the collateral circulation is being established. The second critical period belonged to the third decade. King considered that if a patient survived this period of 'myocardial strain' he had every chance of living to an old age. Abbott (1927) found that of 212 cases reported in the literature, 142 were subjects over one year, while the remaining 70 were newly-born infants.

TABLE I

To Illustrate the Sex and Age Incidence of Congenital Stenosis of the Aortic Arch among 19,217 Cases where the Heart and Aorta were examined at Necropsy (London Hospital)

	Routine necropsies.			Congenital stenosis of the aortic arch.		
Age.	Total.	Male.	Female.	Total.	Male.	Female.
All ages	19,217	11,592	7,625	26	17	9
Under 1 year	3,002	1,743	1,259	15	9	6
Under 1 week	617	344	273	11	7	4
Foetuses	330	169	161	—	—	—

In the present series of 28 cases the average age was 11·4 years. In 11 subjects who had survived infancy the average age was 28·7 years. One patient who had died from pulmonary embolism was 60 years old. Eleven

subjects were infants of seven days or younger, and nine of these were under four days; four were under two days and one was a day old.

Sex. A survey of the literature indicates that congenital stenosis of the aorta is a commoner finding in the male. In Burke's (1901) series of 20 cases there were only three females. Other cases, King (1926), Gossage (1909), Kohn (1911), Weber and Price (1912), Lommel (1919), Frocken (1924), have been recorded where the deformity occurred in the female. In view of this reported high incidence in the male sex, it is instructive to note that in the author's series ten, or over one-third, were females. Further, when the sex incidence of the condition was estimated among 18,887 subjects (foetuses excluded) examined at necropsy it was found to show males 0·15 per cent. and females 0·12 per cent. It follows that this congenital anomaly occurs almost as frequently in females as in males.

Anatomical Varieties

Most writers on the subject of coarctation of the aorta have adhered to the classification adopted by Bonnet (1903), who placed the cases in two groups which he referred to as infantile type and adult type.

In the infantile type he included all cases which demonstrated a diffuse narrowing of the aortic isthmus, and because these often presented other congenital deformities, he regarded the anomaly to be the result of maldevelopment. He believed that when the degree of stenosis was moderate in cases of this class the failure on the part of the isthmus to assume its normal anatomical outline could be attributed directly to some external influence which operated soon or immediately before birth. Théremin's (1895) finding that the aortic isthmus showed some degree of narrowing at the time of birth in 50 per cent. of weakly or premature infants appeared to lend support to this view. In those subjects in this class who exhibited extreme narrowing at the isthmus, Bonnet maintained that the operating cause commenced during embryonic life and that the branchial arch corresponding to the aortic isthmus had failed to develop.

In the adult type he included all cases which demonstrated a more or less abrupt constriction of the aorta at a point not far removed from the site of entry of the ductus arteriosus. He considered that this variety was not met with in the newly-born before closure of the ductus arteriosus had commenced, and that it was an acquired condition and was not the result of faulty development.

A study of the 28 cases recorded in this paper has convinced me of the great difficulty encountered in allotting the cases to one or other of these two groups. Such a classification also necessitates the application of two separate theories as to the cause of processes whose ultimate result is the production of an anatomical deformity essentially similar. To obviate this unnecessary speculation as to the cause of the lesion, I propose to introduce

a classification whereby the cases are allotted to different groups according to the nature of the anatomical deformity present and the arrangement of the associated or compensatory developmental lesions. In this way it has been possible to define *six* separate types of congenital stenosis and atresia of the aortic arch. In order to allocate a case to its particular group it is necessary to consider the following data: 1. The site, nature, and extent of the constriction. 2. Condition of the aorta proximal to the site of stenosis. 3. Patency or otherwise of the ductus arteriosus. 4. Relationship between the systemic and pulmonary circulation. The adoption of this classification will also facilitate the interpretation of certain clinical findings presented by these cases, and more especially will help to explain such appearances as are found on radiological examination of the heart and greater vessels. It will also help to determine the nature of the changes that are the direct result of a modified circulation initiated by the presence of this congenital deformity.

The six types will now be considered separately and a short description of the cases appended.

Type I. *Congenital Stenosis of Aortic Arch. Ductus Arteriosus Patent. Hypoplasia of Proximal Portion of Aorta.* (Fig. 2)

Eight of the 28 cases fall into this group. Four were males and four females. Six were under five weeks old and the remaining two cases were 8 and 30 years respectively. All eight cases were examined at necropsy. The stenosis in all instances occurred in the distal portion of the aortic arch and was placed proximal to the origin of the left subclavian artery in three, and immediately distal to it in five cases. The degree of stenosis was severe in all eight subjects, and as two had survived 8 and 30 years respectively it would appear that the extent of narrowing of the aortic lumen in this group does not directly determine the duration of life. The ductus arteriosus had remained open in all eight cases; its lumen was moderately patent in three and widely patent in five instances. Further reference to patency of the ductus will be made in a later section.

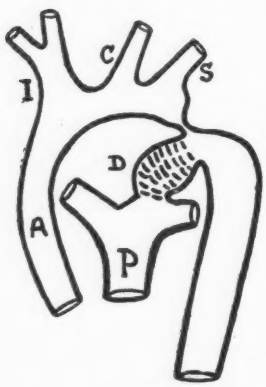

FIG. 2. Diagram to illustrate the greater vessels in cases of congenital stenosis of aortic arch classified as Type I. (A) Aorta; (P) Pulmonary artery; (D) Ductus arteriosus; (I) Innominate artery; (C) Left common carotid artery; (S) Left subclavian artery.

Aorta proximal to the stenosis. Two of the cases demonstrated congenital hypoplasia of that part of the aorta placed proximal to the site of constriction, the vessel being very small, and in one instance rudimentary. In five cases the ascending aorta was considerably smaller than the pulmonary artery. In one case the relative size of the

arteries was not recorded, although the right ventricle was reported to be larger than the left ventricle. The heart chambers were similarly altered in their normal relative dimensions. Congenital hypoplasia of the left ventricle with hypertrophy of the right ventricle and auricle occurred in three cases; the right ventricle was larger than the left in four cases and relatively larger in the remaining case.

TABLE II

Giving Relative Size of the Ventricles and the Greater Vessels in Eight Cases of Congenital Stenosis of the Aortic Arch classified as Type I. The Terms Proximal *and* Distal *refer to the Origin of the Left Subclavian Artery.* > : *Greater than. The Signs in the Final Columns portray Relative Size.* —, *indicates the Presence of Hypoplasia*

Age.	Site of stenosis in relation to origin of left subclavian artery.	Degree of patency of ductus arteriosus.	Condition of aorta proximal to stenosis.	Comparison of size of right and left ventricles.	
				R.V.	L.V.
Two weeks	Proximal	Moderate	Hypoplasia	+	—
30 years	Proximal	Wide	P.A. > Aorta	+ + +	+ +
Two weeks	Distal	Wide	?	+ +	+
Two days	Proximal	Wide	Rudimentary	+ +	+
8 years	Distal	Moderate	P.A. > Aorta	+	—
Five days	Distal	Moderate	P.A. > Aorta	+ +	+
One day	Distal	Wide	P.A. > Aorta	+	—
Five weeks	Distal	Wide	P.A. > Aorta	+ +	+

The recognition of these changes in the anatomical outline of the ascending aorta and the heart chambers is of great importance in the radiological diagnosis of congenital aortic stenosis, and this will be more fully considered when the question of clinical diagnosis is discussed in a later section.

Hypertrophied arteries forming part of an established collateral circulation were not observed in any of the eight cases. It appears that the shunt provided by a patent ductus arteriosus obviates the necessity of establishing a system of arterial anastomosis as found in those cases classified as Types II and III. It is possible, however, that certain rare cases may present stenosis of the aorta associated with only a slight degree of patency of the ductus arteriosus. Such a case has been reported by Ulrich (1932) where hypertrophied arteries forming a collateral circulation were found at necropsy. Although erosion of the ribs was reported on radiological examination of this case, it is noteworthy that no hypertrophied arteries were identified during clinical examination of the chest, and the author draws attention to the absence of certain vascular signs peculiar to other cases of congenital stenosis of the aortic arch. Unfortunately, the dimensions of the lumen of the ductus arteriosus are not recorded.

Case 1. Male, aged two weeks. Necropsy. (*P.M. 280*, 1927.)

Heart failure. Congenital malformation of heart and aortic arch. Aorta, carrying coronary arteries, arising from very small left ventricle (2 × 1·5 cm.; wall, 0·25 cm. thick). No communication between left ventricle and left

auricle, mitral orifice being absent. Patency (0·5 cm. diam.) of interventricular septum. Very large right ventricle (5 cm. diam.) occupying greater part of heart. Pulmonary artery, 2·5 cm. circumf.; wall, 0·06 cm. thick. Very large right auricle representing greater part of auricular area with large appendage receiving venae cavae. Pulmonary veins entering very small left auricle (1·5 × 1·0 cm.) chiefly represented by its appendage. Foramen ovale patent (0·5 cm. diam.) and furnished with valve. Well-formed tricuspid valve separating large right auricle from large right ventricle. Pulmonary artery after giving off right and left pulmonary branches continued along moderately wide ductus arteriosus to form descending thoracic aorta. Greatly narrowed aortic arch (0·15 cm. diam.) passing into descending thoracic aorta proximal to entry of ductus arteriosus. Left subclavian and left vertebral arteries arising from narrow portion of arch. Innominate artery arising from ascending aorta. Left common carotid artery arising from arch just proximal to narrow portion or constriction. Meckel's diverticulum (2 cm. long; 1·7 cm. circumf.) 53 cm. from caecum.

Case 2. Male, aged 30 years. Necropsy. (*P.M. 433*, 1912.)

Heart failure. Congenital stenosis of aortic arch. Very considerable hypertrophy and dilatation of all chambers of heart. Striated thrombus in right auricular appendage. Marked narrowing of aorta between orifices of left common carotid and left subclavian arteries. Marked dilatation with slight thickening of pulmonary artery. Widely patent ductus arteriosus. Numerous fat flecks and streaks of atheroma throughout aortic arch, its branches, and descending thoracic aorta. Succulent yellow cushion of hypertrophy of intima without atheroma in pulmonary artery. Acute and chronic bronchitis. Congestion of emphysematous lungs. Organized infarct in posterior portion of lower lobe of right lung. Accessory fissures in lobes of left lung. Back pressure atrophy with paradoxical lobulation of liver. Back pressure spleen and kidneys. Scarring of upper pole of left kidney. Accessory artery and vein to lower pole of both kidneys. Congestion and mucous catarrh of stomach and intestines. Slight ascites. Bilateral hydrothorax. Hydropericardium. Pitting oedema of genitalia and lower extremities. Cyanosis.

Case 3. Female, aged two weeks. Necropsy. (*P.M. 444*, 1913.)

Broncho-pneumonia. Congenital stenosis of aortic arch. Purulent bronchitis with extensive areas of collapse and few small nodules of peribronchial consolidation throughout both lungs. Great hypertrophy of right ventricle (wall, 0·8 cm. thick). Stenosis (0·5 cm. circumf.) of aortic arch immediately beyond orifice of left subclavian artery. Ductus arteriosus patent (0·8 cm. circumf.). Foramen ovale patent to pencil.

Case 4. Female, aged two days. Necropsy. (*P.M. 352*, 1909.)

Heart failure. Congenital stenosis of aortic arch. Foramen ovale widely patent. Right ventricle larger than left ventricle. Walls of ventricles of equal thickness. Pulmonary artery, after giving off its two pulmonary branches, continued directly through widely patent ductus arteriosus into descending thoracic aorta. Ascending aorta continued into large innominate artery. Left common carotid and left subclavian arteries arising from small rudimentary arch. Aortic arch opening by means of small aperture into descending thoracic aorta at site of insertion of ductus arteriosus.

Case 5. Male, aged 8 years. Necropsy. (*P.M. 250*, 1918.)

Heart failure. Congenital stenosis of aortic arch. Tuberculosis of bronchial glands. Very great hypertrophy and dilatation of right ventricle and right auricle. Hypoplasia of left ventricle and left auricle. Right heart about ten times size of left heart. No congenital malformation of heart. Stenosis (0·35 cm. diam.) of aorta opposite centre of orifice of patent ductus arteriosus (0·5 cm. diam.). Hypertrophy of pulmonary arteries and considerable of pulmonary veins. Numerous small fat flecks of atheroma in aortic arch and its branches. No atheroma of aorta beyond site of stenosis. Very numerous pinhead fat flecks of atheroma in thickened pulmonary arteries. Ascites, 10 oz. Bilateral pleural effusion, 10 oz. each side. Generalized subcutaneous oedema. Oedema and central congestion of liver. Back pressure spleen and kidneys. Severe mucous catarrh of stomach and intestines. Confluent caseous tubercles in bronchial glands in hilum of left lung. Cyanosis.

Case 6. Male, aged five days. Necropsy. (*P.M. 969*, 1911.)

Intestinal obstruction. Congenital abnormalities of greater vessels and jejunum. Operation: iliac jejunostomy. Patent foramen ovale (5 × 4 mm.). Wall of left ventricle, 4·5 mm. thick. Wall of right ventricle, 3·5 mm. thick. Ascending aorta (3 mm. diam.) dividing to form innominate and left common carotid arteries. Aortic arch (3 mm. diam.) arising 3 mm. proximal to this bifurcation. Aortic arch distal to origin of left subclavian artery, 2 mm. diam., but widening opposite entrance of ductus arteriosus (1·5 mm. diam.). Pulmonary artery (8 mm. diam.) giving off large right and left branches and narrowing abruptly to form ductus arteriosus. Right auricle receiving right superior vena cava formed by right internal jugular and right subclavian veins, inferior vena cava, and left superior vena cava formed by left internal jugular vein, left subclavian vein, and left superior vena azygos minor. Left superior vena cava entering auricle by coronary sinus after hooking round to pass behind left pulmonary vein. Jejunum (2·8 cm. diam.) ending abruptly 22 cm. from duodenum in narrow cord (4 cm. long) situated in periphery of mesentery. Bilateral congenital inguinal hernial sacs.

Case 7. Female, aged one day. Necropsy. (*P.M. 682*, 1912.)

Heart failure. Congenital malformation of heart and aorta. Patent foramen ovale (0·2 cm. diam.). Hypertrophy of right ventricle (external transverse measurement, 3 cm., thickness of wall, 0·4 cm.). Hypoplasia of left ventricle (external transverse measurement, 1·5 cm.; thickness of wall, 0·3 cm.). Pulmonary artery, 1·8 cm. circumf. Ascending and descending aorta, 1·6 cm. circumf. Stenosis of aorta (1·1 cm. circumf.) immediately proximal to opening of widely patent ductus arteriosus (1·5 cm. circumf.). Left vertebral artery arising from aortic arch. Bilobed left kidney.

Case 8. Female, aged five weeks. Necropsy. (*P.M. 87*, 1932.)

Heart failure. Congenital stenosis of aortic arch. Foramen ovale patent (0·1 cm. diam.). Great hypertrophy and dilatation of right auricle and right ventricle. Wall of right ventricle, 0·8 cm. thick; wall of left ventricle, 0·6 cm. thick. Pulmonary commissure, 2·8 cm. circumf.; aortic commissure, 1·8 cm. circumf. Oval opening (0·7 × 0·3 cm.) in interventricular septum at junction of middle and lower thirds. Ductus arteriosus patent (0·7 cm. circumf.). Congenital stenosis of aortic arch (0·4 cm. circumf.) immediately above orifice of ductus arteriosus. No other abnormality of vessels.

Type II. *Congenital Stenosis of Aortic Arch. Ductus Arteriosus Closed. Hypertrophy of Proximal Portion of Aorta.* (Fig. 3)

Ten, or more than one-third, of the cases fall into this group. Seven are males and three females. Eight were examined at necropsy and two are alive and in fair health. The two youngest subjects in this group were three and eighteen months old respectively, and the average age of the remaining eight was 30·7 years, so that the expectancy of life would appear to be greater in cases in this group than those in other groups. In the eight cases examined at necropsy the constriction occurred in the aortic arch at a point distal to the origin of the left subclavian artery. The degree of stenosis was moderate in three, severe in five, and apparently severe in Cases 9 and 18. In those instances where the stenosis has been referred to as severe, there was hypertrophy, occasionally accompanied by dilatation, of the left ventricle with hypertrophy of that portion of the aorta proximal to the seat of stenosis. The ductus arteriosus had closed in seven cases; in Case 15 its pulmonary extremity alone had closed and a mycotic aneurysm had formed in its dilated aortic portion and ruptured into the pleura. It would appear that the ductus has also closed in Cases 9 and 18, as there is neither clinical nor radiological evidence of its patency in these two patients.

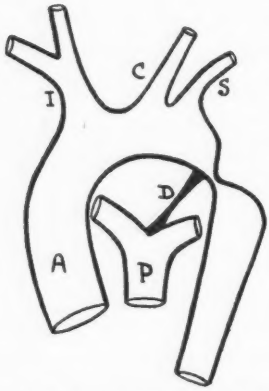

FIG. 3. Diagram to illustrate the greater vessels in cases of congenital stenosis of the aortic arch classified as Type II. (Key as in Fig. 2.)

Case 9. Male, aged 23 years. History and clinical findings.

The patient, a photo-lithographer, is one of two children. His mother and sister are healthy. His father died twelve months ago from pneumonia. At the age of 6 he contracted scarlet fever, and for a short time following the illness he became rather nervous, but soon recovered. He has had no other illness and has in every respect led a normal and active life. There have been no attacks of dyspnoea or cyanosis and there is no history of rheumatic fever, chorea, tonsillitis, headache, or epistaxis. He has never experienced nocturnal frequency of micturition. He first came under the author's observation in June 1930 following an examination by his medical attendant necessitated by the patient's application for a life insurance policy. When re-examined in September 1931 he complained of profuse sweats which came on with the least exertion or excitement. He also complained that after changing from the reclining to the standing position he experienced great discomfort in his legs and feet which resembled the sensation he experiences when the pressure in the armlet of a sphygmomanometer placed around the thigh is released. He considers that this symptom is caused by blood flowing into the limbs to fill the emptied vessels. This sensation is followed by weakness and numbness of the lower extremities which passes off after walking a short distance. He does not usually suffer from

cold feet, but he has noticed that when they do get cold he finds it difficult to restore warmth. *On examination*: A well-nourished youth of good physical development. No signs of hyperthyroidism. No cyanosis. No clubbing of fingers or toes. Tonsils slightly hypertrophied. No abnormal pulsation in pharynx. Pulses equal regular and not collapsing in character. Gross thickening of brachial and radial arteries. Pulsation in femoral arteries

TABLE III

Readings obtained in Case 9 by means of Pachon's Oscillometer

Pressure in armlet expressed as mm. of Hg.	Units of oscillation.	
	In right arm.	In right leg.
300	1	0·5
280	1	0·5
250	1·5	0·5
220	2	1
200	3	3
180	5	4
160	6	4
150	6	4
130	10	6
110	11	5
100	10	4·5
80	7	3
60	4	3
50	4	2
30	3	1
20	3	1
10	3	0·5

difficult to elicit. Brachial blood-pressure: right, 165/95; left, 155/95. Blood-pressure in right lower limb, 145/–. Readings obtained by means of Pachon's oscillometer are recorded in Table III. Greatly dilated, tortuous, and pulsatile vessels (see Plate 1, Figs. 4 and 5) arranged along the posterior and inferior borders of scapulae, in the interscapular region, and along lateral borders of sternum. Branches of transverse cervical, axillary, scapular, aortic intercostal, and internal mammary arteries identified as units forming this network of the collateral circulation. Harsh systolic murmur heard over hypertrophied vessels. Prominent heaving and thrusting pulsation in both anterior triangles of neck. Apex beat forcible and located in fifth intercostal space, $3\frac{3}{4}$ in. to left of mid-line. No thrills and no diastolic shock felt. First sound in mitral area loud and duplicated. Systolic murmur in aortic area conducted to vessels of neck. Short aortic diastolic murmur conducted downwards and to the left as far as the mitral area. No evidence of capillary pulsation. Retinoscopy showed no abnormal pulsation in the retinal vessels. Examination of lungs, abdomen, and central nervous system disclosed no abnormality. No subcutaneous oedema. Urinary analysis showed no abnormal constituent. Wassermann and Kahn reactions negative in blood-serum. Blood count was normal. Orthodiagraphy (Fig. 6) showed enlargement of the left ventricle, absence of the aortic knuckle to the left and prominence to the right of the ascending aorta. It failed to demonstrate discontinuity of the aortic arch in the oblique positions. Teleradiogram (Plate 1, Fig. 7) showed focal areas of erosion of lower border of ribs in their posterior portions. Electrocardiogram demonstrated normal rhythm, no relative preponderance, high amplitude in Leads II and III,

notching of QRS complexes in Lead III and inversion of P-wave in Leads II and III. A tracing of the femoral and radial arterial pulsation (Fig. 8) showed the radial pulse to precede the femoral pulse by 0·1 sec.

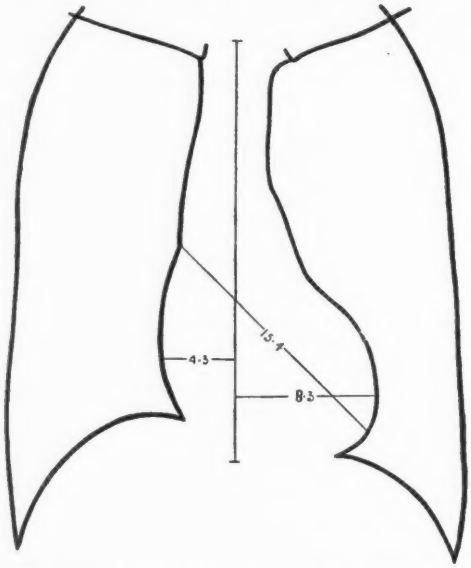

FIG. 6. Orthodiagram in Case 9. Numerals indicate distances in cm.

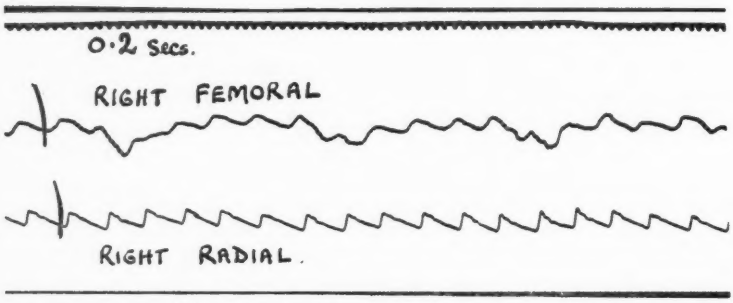

FIG. 8. Tracing of right femoral and radial arterial pulses obtained in Case 9. The three points of depression shown in the femoral tracing indicate the commencement of inspiration.

Case 10. Male, aged three months. Necropsy. (*P.M. 170*, 1914.)

Heart failure. Broncho-pneumonia. Congenital stenosis of aortic arch. Foramen ovale patent (0·1 cm. diam.). Dilatation with some degree of hypertrophy of right ventricle (wall, 0·2 cm. thick). Dilatation and hypertrophy of left ventricle (wall, 0·8 cm. thick). Stenosis of aorta (2·2 cm. circumf.) immediately beyond insertion of ligamentum arteriosum. Microscopical examination of sections of aorta taken above and below constriction showed considerable hypertrophy of media in aorta above stricture. No obvious dilatation of anastomotic vessels between branches of subclavian and intercostal arteries. Purulent bronchitis with areas of peribronchial consolidation

and collapse in middle and lower lobes of right lung. Oedema of liver, kidneys, and stomach. Ascites, 1 oz. Bilateral pleural effusion, 1 oz. each side. No clubbing of fingers. No cyanosis.

Case 11. Male, aged 16 years. Necropsy. (*P.M. 915*, 1917.)

Broncho-pneumonia. Congenital stenosis of aortic arch. Foramen ovale closed. Hypertrophy of left ventricle. Great constriction (admitting fine probe) of descending aorta just below origin of first pair of bronchial arteries. Great hypertrophy of internal mammary arteries. Flecks of atheroma in ascending aorta and arch, none in aorta distal to seat of constriction. Bilateral fibrinous pleurisy. Purulent bronchitis with areas of pneumonic consolidation and collapse in lower lobe of left lung.

Case 12. Male, aged 60 years. Necropsy. (*P.M. 412*, 1930.)

Pulmonary embolism. Thrombosis in venae comites of meningeal arteries. Thrombosis in arteries of lower limbs. Congenital stenosis of aortic arch. Carcinoma of pylorus. Foramen ovale closed. Brown atrophy of myocardium with two areas of fibrosis (0·2 × 0·15 cm. diam. × 1 cm. long) beneath endocardium of anterior papillary muscle of mitral valve. Cusps of aortic valve, normal. Great narrowing of lumen of aorta at site of insertion of ligamentum arteriosum with irregular focal calcification at site of narrowing. Diffuse dilatation (up to 9 cm. circumf.) of upper 6 cm. of descending thoracic aorta with slight thinning of its wall in this region (0·07 cm. thick) and less of anterior part of arch (8 cm. circumf.). Ascending aorta, 7 cm. circumf. Lower part of descending thoracic aorta, 5 cm. circumf.; wall, 0·15 cm. thick. First and second pairs of intercostal arteries arising from dilated upper portion of descending thoracic aorta below constriction, showing enlarged orifices (upper pair, 0·65 cm. diam.; lower pair, 0·40 cm. diam.). No evidence of erosion of ribs examined at necropsy. Left vertebral artery taking origin from aortic arch between left common carotid and left subclavian arteries. Moderate atheroma: fatty buttons on mitral cusps, commissure, and in coronary arteries; flecks in ascending aorta, arch, and its branches; confluent fatty buttons at bifurcation of carotid arteries (partly calcified in left carotid); flecks, buttons, and ulcerated calcareous plaques at origin of innominate artery and at site of insertion of ligamentum arteriosum. No atheroma in descending thoracic aorta and only few small flecks in abdominal aorta. Atheromatous ulcer in both common iliac arteries. Carcinomatous ulcer on anterior wall of pylorus. Considerable stenosis of pyloric sphincter. Secondary carcinomatous deposits in glands and liver. Recent ante-mortem thrombus in posterior trunk of right internal iliac artery. Ante-mortem thrombus filling right profunda femoris for distance of 6 cm. from its origin. Coiled embolus in right main pulmonary artery and in branch of left pulmonary artery to lower lobe. Ante-mortem thrombus in both venae comites of left middle meningeal artery in its intracranial course, and in both cavernous sinuses. Extreme wasting.

Case 13. Female, aged eighteen months. Necropsy. (*P.M. 506*, 1913.)

Heart failure. Broncho-pneumonia. Foreign body in bronchus. Congenital stenosis of aortic arch. Purulent bronchitis, bronchiectasis and nodules of peribronchial consolidation and collapse throughout lower lobe, posterior part of upper lobe of right lung, and greater part of lower lobe of left lung. Small bronchiectatic abscesses in lower lobe of right lung. Eroded portion

of fish-bone (1·5 × 0·1 cm.) lodged in bronchus of second degree in lower lobe of left lung. Foramen ovale closed. Circular constriction in aorta at site of insertion of ligamentum arteriosum. Minute fat flecks of atheroma at base of mitral valve. Cloudy swelling of myocardium. Oedema and severe parenchymatous degeneration of liver and kidneys. Severe mucous catarrh of stomach. Grey granular thrombus in posterior two-thirds of superior longitudinal sinus and in adjacent 2 cm. of both lateral sinuses.

Case 14. Male, aged 35 years. Necropsy. (*P.M. 44*, 1909.)

Haemopericardium. Rupture of mycotic aneurysm of aorta. Congenital stenosis of aortic arch. Haemopericardium (25 oz. of recent red blood clot). Acute fibrinous pericarditis. Septic erosion of small pyogenic saccular aneurysm of aorta immediately above aortic commissure. Vegetations on rugged upper margin of aneurysm. Congenital stenosis of aorta at site of insertion of ligamentum arteriosum. Constriction only admits fine probe. Great hypertrophy and dilatation of left ventricle. Thickening of aortic valves with calcification of attached border. Fusion of right and left anterior aortic cusps. Foramen ovale closed. Few small streaks of atheroma in ascending aorta and aortic arch. Minute flecks of atheroma in descending thoracic, and abdominal aorta. Small patch of atheroma in right middle cerebral artery. Moderate hypertrophy of carotid arteries. Great hypertrophy and dilatation of subclavian arteries with established collateral circulation through posterior scapular, and especially through internal mammary arteries. Septic spleen. Small anaemic infarct in left kidney. Acute nephritis. Bilateral pleural effusion. Ascites. Generalized subcutaneous oedema. (*Note*: This case was cited by Turnbull (1914) as an example of non-granulomatous arteritis of large elastic arteries.)

Case 15. Female, aged 6 years. Necropsy. (*P.M. 121*, 1922.)

Haemoptysis. Broncho-pneumonia. Rupture of mycotic aneurysm of ductus arteriosus into lung. Congenital stenosis of aortic arch. Chronic abscess in middle lobe of right lung with focal empyema. False aneurysm (7 cm. diam.; wall, up to 0·4 cm. thick) beneath pericardium in front and to left of roots of great vessels lined by trabeculated organized blood-clot, and containing dense laminated blood-clot. Aortic orifice of ductus arteriosus (0·7 × 0·4 cm.) opening into funnel-shaped, smooth-lined, true aneurysmal dilatation (2 cm. diam.) of aortic portion of ductus arteriosus with sharply-cut free edges projecting into false aneurysm. Pulmonary end of ductus arteriosus closed. Portion of dorsal wall of bifurcation of pulmonary artery adherent to lower anterior border of false aneurysm and showing area of great thickening (1·5 × 1·0 cm.) covered by layer of thrombus. Small area of thrombosis on pulmonary intima, 1 cm. beyond this. Purulent infiltration (Gram-positive diplococci) of wall of ductus arteriosus, wall of false aneurysm, and adjacent pulmonary artery. Aneurysm adherent to anterior part of mesial aspect of upper lobe of left lung and eroding lung substance to depth of 1·0 cm. Organized fibrous obliterating pericarditis; adhesions most dense over left auricle. Foramen ovale closed. Slight hypertrophy of heart, chiefly involving right side. Narrowing of aortic arch. Ascending aorta, 4·3 cm. circumf.; descending thoracic aorta, 2·8 cm. circumf. Very slight atheroma. Oedema and haemorrhage consolidating upper and anterior one-fourth of upper lobe of left lung around perforation. Oedema and collapse of lower border of upper lobe of right lung. Blood in trachea and main bronchi.

Bright yellow, partly inspissated creamy pus (few Gram-positive diplococci and short streptococci) in honeycombed fibrosis of anterior border of middle lobe of right lung continuous with empyema (4·5 × 3·0 cm.) placed between anterior extremity of upper and middle lobes of right lung and chest wall. Double pelvis with double ureter uniting immediately before entry into urinary bladder on right side.

Case 16. Male, aged 23 years. Necropsy. (*P.M. 513*, 1926.)

Heart failure. Aortic incompetence. Subacute bacteraemic endocarditis. Congenital malformation of heart and aorta. Foramen ovale closed. Great hypertrophy and dilatation of left ventricle. Moderate hypertrophy of other chambers. Severe parenchymatous degeneration of myocardium. Aperture (0·7 cm. diam.) with smooth white fibrous lining filled with soft vegetation between right and left ventricle. Very irregular wrinkled opaque greenish-yellow vegetations (from pinhead up to 2·5 × 1·7 × 1·0 cm. high) scattered over all aspects of aortic cusps, especially ventricular aspect; a few on adjacent mural endocardium with ulceration (0·5 cm. deep) and two filling ulcers (0·5 cm. diam.) in commissure. Vegetations filling somewhat smooth-lined aneurysm (1·5 cm. diam.) in anterior part of base of aortic cusp of mitral valve. Two cusps to aortic valve. No evidence of fibrotic endocarditis in thin translucent part of posterior aortic valve unaffected by vegetation. Considerable destruction of common right and posterior cusp. No abnormality of mitral and tricuspid valves. One vegetation (0·5 cm. diam.) in middle of posterior pulmonary cusp. Abrupt constriction of commencement of descending thoracic aorta. Lumen at this site just admitting probe (0·2 cm. diam.). Considerable atheroma in and around this orifice. Recent ante-mortem thrombus filling orifice. Large (3·5 cm. circumf.) and thin (0·05 cm. thick) left subclavian artery. Large (1·5 cm. circumf.) artery uniting left subclavian artery and descending thoracic aorta beyond stricture and corresponding with site of first intercostal artery. Descending thoracic (3·8 × 0·07 cm.) and abdominal (2·4 × 0·05 cm.) aorta small and thin. Numerous flecks of atheroma in coronary arteries, a few in commissure and ascending aorta, numerous in left subclavian artery; powdered streaks in both common carotid arteries and in right subclavian artery; very faint in upper portion of descending thoracic aorta. Mucopurulent bronchitis in posterior parts of very indurated brown lungs. Haemorrhagic pyaemic abscess (1·5 cm. diam.) in lower border of upper lobe of left lung. Chronic septic spleen. Small partly scarred infarcts in congested kidneys. No clubbing of fingers. Slight anasarca. Pericardial effusion, 4 oz. Ascites, 1 oz.

Case 17. Male, aged 38 years. Necropsy. (*P.M. 244*, 1932.)

Haemorrhage into pericardial adhesions. Recent rupture of lined aneurysm formed by rupture of ascending aorta. Congenital stenosis of aortic arch. Foramen ovale closed. Dense oedematous fibrous pericardial adhesions over left auricle and ventricle. Haemorrhagic infiltration of similar adhesions over right auricle and ventricle, and apex of left ventricle. Lined false aneurysm forming a sac (8 cm. from above down and 9 cm. in circumference) in front and to right of ascending aorta, with extension (7 cm. diam.), filled with clot, behind and to left of right auricle and ventricle. Calcification of greater part of wall of aneurysm. Ragged rupture (2·5 cm. long) in right postero-inferior angle of extension, leading into

haemorrhagic area of pericardial adhesions. Multiple infractions of medial elastic, fibrotic thickening of adventitia and fibrosis and atheroma of hypertrophied intima of ascending aorta. Aortic arch, beyond origin of left common carotid artery, 4 cm. circumf. Abrupt narrowing of aorta (barely admitting a probe, 0·2 cm. diam.) 2·5 cm. beyond left subclavian artery. Dilatation of descending thoracic aorta (5 cm. circumf.) immediately beyond constriction. Abdominal aorta, 3·4 cm. circumf. Great dilatation of subclavian arteries (right, 4·0 cm., left, 3.5 cm. circumf.). Very wide internal mammary arteries (0·6 cm. diam., see Plate 2, Figs. 9 and 10). Widening of commencement of upper intercostal arteries (up to 0·4 cm. diam.). No erosion seen in third, fourth, fifth, and sixth right ribs. Great dilatation and tortuosity of anterior spinal artery from seventh cervical to seventh thoracic segments with unusually large and prominent branches. Slight atheroma in aorta distal to constriction. Ductus arteriosus closed. Left pleural effusion, 2 oz. Ascites, 8 oz. Back pressure congestion of liver, spleen, and kidneys. Wassermann reaction in ante- and post-mortem blood-serum was negative.

Case 18. Female, aged 45 years. History and clinical findings.

The patient was referred to the Cardiac Department, London Hospital, on account of pain and swelling in wrist-joints, shortness of breath on exertion, palpitation, and indefinite slight pain in left side of chest. There was no history of rheumatic fever or chorea. Patient has two healthy children ; there were six still-births. She has never experienced numbness or discomfort in the lower limbs when changing from the reclining to the standing position. No frequency of micturition. Never medically examined in childhood.

On examination (June 1932): A well-nourished woman of moderate physical development. No evidence of hyperthyroidism. No cyanosis. No clubbing of fingers or toes. Tense swelling of tendon sheaths over dorsum of both hands ; slight periarticular swelling of wrists, but movements almost painless. Pulses, equal regular and not collapsing in character. Brachial and radial arteries considerably thickened. Prominent pulsation in neck and inner aspect of upper arms. Femoral pulsation not elicited. Right and left brachial blood-pressure, 205/120. Right femoral blood-pressure, 85/–. Conspicuous pulsation in prominent hypertrophied and tortuous vessels forming collateral circulation over the back of the chest. No pulsation seen over internal mammary arteries. Harsh systolic murmur heard in right suprascapular region and less loud in left. Apex-beat located in fifth left intercostal space, internal to mid-clavicular line ; impulse not unduly forcible. Duplication of second sound in mitral area. Localized systolic murmur heard to the left of the midline in lower third of sternum. Second sound in aortic area duplicated and greatly accentuated. No abnormal physical signs in other systems. Urine analysis showed no abnormal constituent. Wassermann reaction in blood serum, negative. Electrocardiogram showed normal rhythm, no relative preponderance and sharp inversion of T-wave in Lead III. Orthodiagram and teleradiogram (Plate 3, Fig. 12) showed enlargement of left ventricle and loss of prominence of aortic knuckle to the left. Undue prominence of the ascending aorta to the right. Examination in the oblique positions failed to demonstrate discontinuity of the aortic arch. Focal areas of erosion of inferior border of ribs in their posterior portions.

Type III. *Congenital Atresia of Distal Portion of Aortic Arch. Ductus Arteriosus Closed. Hypertrophy of Proximal Portion of Aorta.* (Fig. 13)

Case 19 illustrates how a patient presenting actual atresia of the distal portion of the aortic arch may survive adult life. In the rare cases that make up this group, the left ventricle and that part of the aorta which remains proximal to the site of atresia undergo great hypertrophy and, as the ductus arteriosus has closed, the network of hypertrophied arteries form-

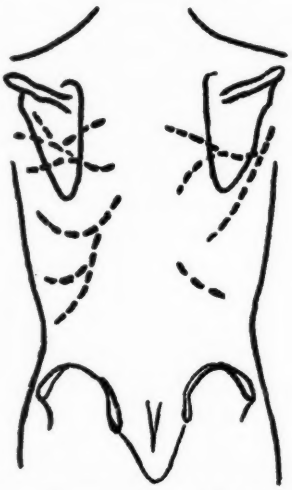

FIG. 11. Diagram showing distribution of main vessels forming collateral circulation in Case 18.

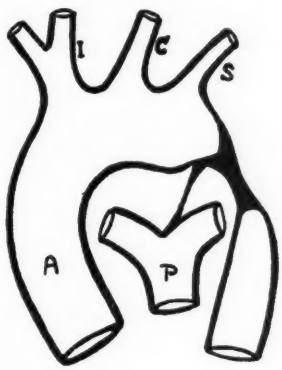

FIG. 13. Showing condition of the greater vessels in cases demonstrating atresia of the aorta and classified as Type III. (Key as in Fig. 2.)

ing the collateral circulation also becomes a prominent feature of this group. Apart from actual obliteration of the aortic lumen, Case 19 resembled in all other respects the cases listed under Type II, and therefore it differs from that group only in the extent or degree of constriction which has occurred in the aorta.

Case 19. Male, aged 32 years. Necropsy. (*P.M. 60*, 1910.)

Heart failure. Aortic incompetence. Acute rheumatic endocarditis. Atresia of aortic arch. Foramen ovale closed. Great hypertrophy of left and right heart chambers with considerable dilatation of left ventricle. Two cusps to aortic valve. Few recent vegetations on slightly thickened aortic valve. Great dilatation of commissure, ascending aorta, and arch. Ligamentum arteriosum not identified. Collateral circulation established by wide arteria aberrans uniting first and second intercostal and subclavian arteries and very tortuous long thoracic arteries. Brachial arteries, 0·3 cm. diam.; femoral arteries, 0·4 cm. diam. Few flecks of atheroma in dilated portion of aorta. Large fatty ridges in widened carotid arteries. Fat flecks in subclavian arteries and in aorta immediately below seat of atresia. Severe atheroma of cerebral arteries. Numerous fat flecks throughout hypertrophied internal

mammary arteries. Few small flecks in thickened pulmonary arteries. Haemorrhagic infected infarcts in both lungs. Purpuric eruption over shoulders and on feet. Oedema of lower extremities.

Type IV. *Interruption of Aortic Arch in its Distal Portion. Ductus Arteriosus widely Patent. Hypoplasia of Proximal Portion of Aorta.* (Fig. 14)

Three cases, two males and one female, are included in this group. Their ages were three, eleven, and two days respectively. Interruption of the aortic arch in its distal portion was present in all three subjects, and it was not possible to trace any connexion between the aortic arch and the pulmonary-ductus-descending aorta trunk. The origin of the arterial branches normally arising from the aortic arch differed in each of the cases. In Case 20, the right and left common carotid arteries took origin from the rudimentary aortic arch, while both subclavian arteries arose from the arterial trunk distal to the site of interruption of the arch. The small innominate and left common carotid arteries were given off by the hypoplasic aortic arch in Case 21, whilst the small left subclavian artery came from the upper extremity of the descending thoracic aorta. In Case 22 all three main arterial trunks had taken origin from the aortic arch proximal to the site of its interruption. In this group the pulmonary artery is continued into the descending thoracic aorta through a widely patent ductus arteriosus. A careful inspection of the intima of that segment of the arterial trunk which marks the ductus arteriosus is equally important in the identification of the larger vessels in cases which belong to Type IV. Complete interruption of the aortic arch as illustrated by Cases 20, 21, and 22, is a rare condition, and Abbott (1927), in a survey of the literature, was only able to refer to five cases which demonstrated this congenital anomaly.

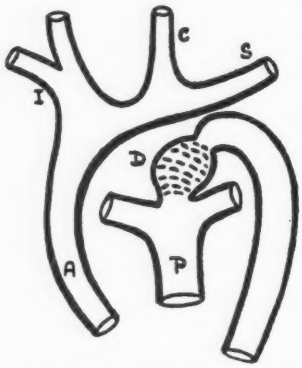

FIG. 14. Arrangement of the greater vessels in cases of congenital interruption of the aortic arch classified as Type IV. (Key as in Fig. 2.)

Case 20. Male, aged 3 days. Necropsy. (*P.M. 555*, 1911.)

Heart failure. Congenital abnormality of aorta. Foramen ovale patent (8·0 × 5·5 mm.). Deficiency (9 mm. diam.) in upper portion of interventricular septum. Wall of right ventricle, 4·0 mm. thick; wall of left ventricle, 4·5 mm. thick. Hypoplasic ascending aorta dividing to form right and left common carotid arteries. Coronary arteries arising from sinuses of Valsalva. Large pulmonary artery continued into descending thoracic aorta through widely patent ductus arteriosus and giving origin to right and left subclavian arteries. No communication between aortic arch and pulmonary artery. No abnormality in veins. Small post-anal dimple.

Case 21. Female, aged 11 days. Necropsy. (*P.M. 389*, 1911.)

Heart failure. Congenital abnormality of aorta. Patent foramen ovale. Right internal jugular, right axillary, and right azygos veins opening into superior vena cava. Corresponding veins on left side opening into horn of right auricle. Interventricular septum patent in this upper and anterior portion. Hypoplasic aorta confined to trunk giving origin to innominate and left common carotid arteries. Pulmonary artery continued as descending thoracic aorta through widely patent ductus arteriosus. Small left subclavian artery arising from upper extremity of descending thoracic aorta.

Case 22. Male, aged 2 days. Necropsy. (*P.M. 124*, 1931.)

Heart failure. Congenital abnormality of aortic arch. Foramen ovale patent (0·7 cm. diam.). No other abnormality of heart chambers. Pulmonary artery, after giving off right and left pulmonary branches 1·0 cm. from its commencement, continued through widely patent ductus arteriosus into descending thoracic aorta. Aorta ending abruptly after giving off innominate, left common carotid, and left subclavian arteries. No trace of connexion between aorta and descending thoracic aorta. Four splenunculi (from 0·2 to 0·7 cm. diam.) in hilum of spleen.

Type V. *Congenital Atresia of Proximal Portion of Aortic Arch. Ductus Arteriosus Patent.* (Figs. 15 and 16)

Five cases, three males and two females, are placed in this group. All five were examined at necropsy. The condition is not compatible with long life,

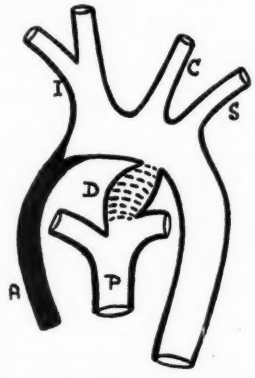

FIG. 15. Diagram to illustrate the first variety of the deformity found in cases classified as Type V. (Key as in Fig. 2.)

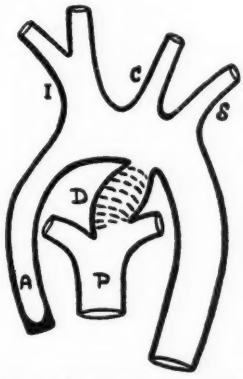

FIG. 16. Diagram to illustrate the second variety of the deformity found in cases classified as Type V. (Key as in Fig. 2.)

and the ages of the cases cited here were 7, 3, 4, 4, and 3 days respectively. In two instances (Cases 23 and 24) there was complete atresia of the entire length of the ascending aorta (Fig. 15), this portion of the aorta being represented by a fibrous cord. This was associated with hypoplasia of the left ventricle and relative enlargement of the right ventricle. The atresia in Cases 25, 26, and 27 did not involve the whole extent of the limb of the

ascending aorta, but was confined to the aortic opening (Fig. 16), the remaining portion of the ascending aorta being represented by a rudimentary vessel with a narrow lumen. In this way the proximal part of the aorta formed a cul de sac or ampulla from which the coronary arteries took origin. In Case 26 a very small left auricle communicated with a large right auricle by means of a patent foramen ovale, and the right auricle opened into a single ventricle whence the pulmonary artery took origin. In all five cases the blood to the great vessels arising from the aortic arch, and also to the descending thoracic aorta, was conveyed from the right ventricle through the pulmonary artery and thence through a widely patent ductus arteriosus. In some instances this modification in the structure and function of these vessels had given to the pulmonary-ductus trunk a uniform calibre and the appearance of the true aortic arch. An interpretation of the anatomical anomaly rests with the tracing of the vessels from their respective sources in the heart chambers, and this is facilitated by a close study of the intima of the arterial trunk and the identification of the commencement of the coronary arteries. That portion which represents the ductus arteriosus shows the characteristic smooth velvety and raised transverse ridges.

Case 23. Male, aged 7 days. Necropsy. (*P.M. 285*, 1911.)

General fibrinous peritonitis. Haemoperitoneum. Operation: colostomy. Congenital atresia of colon and aorta. Foramen ovale patent to probe (0·2 cm. diam.). Interventricular septum patent in its upper portion. Atresia of conus arteriosus. Pulmonary artery continuous with aorta through persistent ductus arteriosus. Right pulmonary artery greater than left. Innominate and left common carotid arteries arising from common arterial stem. Hypertrophy of bronchial arteries. Colon ending in blind sac and continued as fibrous cord $2\frac{1}{2}$ in. from anus. Conspicuous post-anal dimple. Bilateral syndactyle. Cleft soft palate. (No mention made of coronary arteries.)

Case 24. Male, aged 3 days. Necropsy. (*P.M. 424*, 1914.)

Heart failure. Congenital atresia of aorta. Foramen ovale patent. Minute left ventricle communicating by means of patent interventricular septum with large right ventricle. Small left auricle with narrow mitral orifice. Atresia of ascending aorta, represented as fibrous cord. Widely patent ductus arteriosus. (Origin of coronary arteries not noted.) Congestion and partial atelectasis of lungs. Well-developed infant.

Case 25. Male, aged 4 days. Necropsy. (*P.M. 44*, 1920.)

Heart failure. Congenital malformation of heart and aorta. Small left auricle communicating with dilated right auricle by means of widely patent foramen ovale. Small mitral orifice. Cavity of left ventricle measuring only 0·5 cm. across. Complete atresia of aortic cusps. Ascending aorta represented by narrow vessel (0·5 cm. circumf.). Great dilatation of right ventricle. Wide pulmonary artery (3·6 cm. circumf.) communicating through widely patent ductus arteriosus with aortic arch. (Origin of coronary arteries not noted.) Gross subarachnoid haemorrhage over frontal lobes.

Case 26. Female, aged 4 days. Necropsy. (*P.M. 169*, 1909.)

Broncho-pneumonia. Congenital malformation of heart and aorta. Foramen ovale (0·8 × 1·4 cm.) forming only opening of very small left auricle into heart cavity. Large right auricle communicating by single opening with single ventricle. Opening guarded by continuous valve with pulmonary artery arising anteriorly. Pulmonary artery guarded by valve with three cusps giving off (0·7 cm. from its commencement) its two pulmonary branches and continued through patent ductus arteriosus into descending thoracic aorta. Constriction, and adjacent to this an opening into rudimentary ascending aorta and arch placed 0·7 cm. distal to origin of two pulmonary branches. Atresia of proximal end of ascending aorta forming closed ampulla. Coronary arteries arising from ampulla. Innominate, left common carotid, and left subclavian arteries arising from rudimentary aortic arch.

Case 27. Female, aged 3 days. Necropsy. (*P.M. 236*, 1931.)

Heart failure. Congenital malformation of heart and aorta. Foramen ovale patent. Cavity of left ventricle very small (0·7 cm. diam.). Great hypertrophy of right ventricle forming greater bulk of heart. Complete atresia of aortic orifice. Three small sinuses of Valsalva present; aortic cusps fused together at contact margins. Coronary arteries arising normally immediately above sinuses. Ascending aorta, 1·7 cm. circumf. Ductus arteriosus widely patent (0·9 cm. circumf. at its pulmonary end and 2·0 cm. circumf. at its aortic end). Left vertebral artery arising from aorta.

Type VI. *Congenital Absence of Ascending Aorta. Ductus Arteriosus Patent.* (Fig. 17)

Case 28, which is more fully described below, is an example of *cor biloculare*, which is a rare congenital anomaly. Abbott (1928) refers to only ten recorded cases. In the case cited here, the pulmonary artery was continued through a widely patent ductus arteriosus to form the 'arch' and descending thoracic aorta. Stenosis of the 'arch' had occurred at a point immediately distal to the ductus arteriosus.

FIG. 17. Showing distribution of the greater vessels in cases classified as Type VI. (Key as in Fig. 2.)

The case also presented another rare congenital anomaly: the four great branches of the aortic arch took origin from one common arterial trunk. Freyberger (1898) reported a case in whom the right subclavian, right common carotid, thyroidea ima, and left common carotid arteries arose from a common trunk. He expressed a view that it was a comparatively frequent occurrence and was the normal condition in most apes. Freyberger's case, however, is not a true example of a common brachio-cephalic trunk as the left subclavian artery took origin from the descending aortic arch as in the normal subject. Case 28 is a true example of the anomaly and, since this was associated with a *cor biloculare*, I believe that this case is unique.

Case 28. Male, aged 2 days. Necropsy. (*P.M. 39*, 1923.)

Heart failure. Congenital malformation of heart and aorta. Heart consisting of single ventricle opening by means of orifice (3·0 cm. circumf.) guarded by three well-developed semilunar valves and occupying position of pulmonary valve, into single arterial trunk. Two pulmonary branches arising from this vessel, 1·2 cm. distal to valve. Vessel arching upwards, to left and backwards in manner of aorta and presenting gelatinous thickening of its intima (ductus arteriosus) for distance of 1·5 cm. Vessel narrowing to 1·2 cm. circumf. immediately beyond ductus. Common trunk (1·0 cm. diam.) arising from summit of arch and dividing, 1·0 cm. from its origin, into innominate, left common carotid, and left subclavian arteries. Single auricle with two appendages receiving superior and inferior venae cavae on right side and pulmonary veins on left side. Upper edge of interauricular septum present. Auricle opening into ventricle by means of valve with three well-formed cusps. Anterior descending and right coronary arteries arising from innominate artery. No other congenital abnormalities.

Other Congenital Anomalies associated with Congenital Stenosis of Aortic Arch

A consideration of the incidence of other developmental abnormalities in cases of congenital stenosis of the first part of the aorta is important in that it may help to determine the true cause of the condition. Should the incidence of other congenital anomalies which have occurred independently of the aortic lesion appear high in these cases, then strong evidence has been advanced in favour of the view that this deformity of the aorta is likewise the result of faulty development. It is intended here to deal only with the author's cases, as the literature on the subject has been fully and efficiently dealt with by Abbott (1928). Further, it was found difficult in this connexion to apportion the true value and significance of the findings of other authors who have adopted the classification used by Bonnet (1903) and have been compelled to refer to the infantile type as occurring not infrequently in adults, and the adult type as occurring in infants.

It is evident from Table IV that, in those cases referred to as Type II, the presence of other congenital deformities was a rare finding. This does not support the view held by many that the deformity of the aorta in such cases cannot be the result of maldevelopment, for the cases classified as Type I are also examples of Bonnet's adult type, and as seen in the Table the incidence of other congenital abnormalities in this group is high.

The foramen ovale had remained patent in 15 or 57·7 per cent. of the cases, and in eight of these (53·3 per cent.) the opening was wide. Thompson and Evans (1930) found the foramen ovale to be patent in 35 per cent. of 1,100 consecutive necropsies. In only 6 per cent. of these did they find it to be widely open. A comparison of these figures illustrates the high incidence of this congenital abnormality in cases of malformation of the aorta, and also emphasizes the relative frequency with which the foramen had remained widely open. In Case 28 the interauricular septum was represented by a mere ridge.

The ductus arteriosus had remained patent in 17 of the 26 cases examined after death. A separate study was made of cases where necropsy had revealed patency of the ductus. In 7,522 consecutive necropsies (108 of them being infants under seven days old) the ductus was found to be patent in 201, or 2·6 per cent., cases. Most of these were infants; 179 were subjects of three months or under, while 147 were under one month old. Fourteen

TABLE IV

Showing Incidence of Congenital Anomalies other than Stenosis of the Aortic Arch in the Six Types *referred to in the Context*

Nature of associated or independent congenital lesion.	Cases of congenital stenosis of arch showing other congenital lesions.						
	Total.	Type I.	Type II.	Type III.	Type IV.	Type V.	Type VI.
Patent foramen ovale	15	5	1	—	3	5	1
Patent interventricular septum or other deformity of heart chambers	7	2	—	—	2	2	1
Deformity of aortic cusps	6	—	1	—	—	5	—
Patent ductus arteriosus	17	8	—	—	3	5	1
Abnormal origin of branches of aorta	8	3	1	—	1	2	1
Abnormal distribution of veins	3	2	—	—	1	—	—
Atresia of jejunum	1	1	—	—	—	—	—
Atresia of colon	1	—	—	—	—	1	—
Syndactyle	1	—	—	—	—	1	—
Cleft palate	1	—	—	—	—	1	—
Post-anal dimple	2	—	—	—	1	1	—
Meckel's diverticulum	1	1	—	—	—	—	—
Accessory fissures in lungs	1	1	—	—	—	—	—
Bilobed kidney	1	1	—	—	—	—	—
Double renal pelvis and ureter	1	—	1	—	—	—	—
Splenunculi	1	—	—	—	1	—	—
Hernial sacs	1	1	—	—	—	—	—

occurred in subjects over 1 year old, three were over 17 years, and the oldest case was 45 years old. Scammon and Norris (1918), in a statistical summary of the data concerning the conditions which influenced the obliteration of the ductus arteriosus, concluded that a gradual reduction in the size of the lumen commenced at the time of birth and culminated in its closure and obliteration six to eight weeks after birth. This would indicate that the patency of the ductus in the majority of the 179 cases referred to might only signify a delay in the normal physiological process.

Patency of the interventricular septum in its upper portion was found in five cases, in its lower portion in one case, while in Case 28 the septum was not demonstrable, a single ventricle being present. Four cases showed hypoplasia of the left ventricle.

Deformity of the aortic cusps was found in six cases. In three instances there was fusion of the aortic cusps with atresia of the aortic opening. In two cases there was atresia of the whole length of the ascending aorta. In a sixth case there were two instead of three cusps.

Arteries arising from the aorta proved to have an abnormal origin in eight cases. The left vertebral artery took its origin from the aorta in four cases. The right subclavian artery was found to arise from the descending thoracic aorta in one case. This anomaly was also present in a case recently reported by East (1932). The ascending and right coronary arteries in one instance came from the innominate artery. In another case the innominate, left common carotid, and left subclavian arteries arose from a common arterial stem. Accessory renal arteries were present in one case. Examination of the heart and aorta in 7,522 consecutive necropsies disclosed an abnormal origin to the larger arterial branches in nineteen cases. The abnormalities found consisted of the following: left vertebral artery from the aortic arch in three cases, right subclavian artery arising beyond the left subclavian artery and passing behind the oesophagus in twelve cases, left common carotid artery arising from the innominate artery in two cases, accessory right common carotid artery present in one case, and the coronary arteries arising abnormally high from the ascending aorta in another case. The incidence of abnormal origin of branches of the aortic arch is, therefore, relatively higher in those cases where deformity such as congenital stenosis exists in the arch itself.

Abnormality in the distribution of the larger veins emptying into the right auricle appeared in three cases.

Other congenital abnormalities occurring in twenty-six cases consisted of atresia of jejunum, atresia of colon, syndactyle, cleft palate, post-anal dimple, Meckel's diverticulum, accessory fissures in lobes of lungs, bilobed kidney, double renal pelvis and ureter, splenunculi, and hernial sacs. The respective Types which exhibited these anomalies are indicated in Table IV.

Pathogenesis

The difficulty experienced in assessing the influence which the closure of the ductus arteriosus may exert in bringing about this deformity of the first portion of the aorta has introduced much controversy concerning the true pathogenesis of the condition. In the main two theories concerning its etiology have gained favour. The one is known as the paulo-post-natal, or skodaic theory, and the other is based on the assumption that the lesion is the result of faulty development.

As Abbott (1928) has pointed out, although the former theory received the support of Skoda, the credit for formulating the theory is due to Craigie (1841), who recorded his views on the etiology of the condition in a paper reporting a case of stenosis of the aorta adjacent to the site of insertion of the ductus arteriosus. He considered that the obliterating process which occurred in the ductus had been continued into the aorta and produced constriction of that vessel. Such a theory, however, assumes the extension of the tissue of the ductus into the adjacent wall of the aorta, and that this

special tissue contracts after birth in common with that of the ductus. Although in itself an attractive theory, it remains unsupported by any real evidence, and it appears that the ductus tissue has never been found to extend in this way into the wall of the aorta. Klotz (1907), who conducted a microscopical study of the changes occurring in the ductus and aorta at birth, summarized his observations as follows: 'I could never convince myself that there were in the aorta any tissue changes as a result of alteration of the foetal circulation.' Microscopical examination of the aorta adjacent to the site of constriction in Case 10 showed no abnormality other than hypertrophy of that portion of the aorta proximal to the lesion.

It was Reynaud (1828) who first suggested that stenosis of the aortic arch was the result of faulty development and arose during embryonic life.

A study of the cases discussed in this paper has convinced the author of the validity of Reynaud's suggestion, and in support of this view it has been possible to marshal certain facts which have issued from the present investigation, and which appear to lend confirmation to the view that each of the six types of deformity of the aorta described here has been established as the result of congenital maldevelopment. It is convenient at this stage to enumerate these facts:

1. In some of the cases the constriction occurred at some little distance from the site of insertion of the ductus arteriosus, and it is difficult in these cases to see how the ductus could have acted as an etiological factor in the production of the deformity. In Case 15 the ductus had remained patent at its aortic extremity while the pulmonary end was closed; the constriction, nevertheless, in this case had occurred in the aorta and not in the pulmonary artery.

2. The same type of deformity and abrupt constriction of the aorta existed in cases where the ductus had remained widely patent as in those where the ductus had closed.

3. Although most of the associated congenital anomalies were also cardiovascular, no good reasons can be found for linking them causally with the aortic lesion or with patency of the ductus arteriosus. Moreover, the frequency of other non-cardiovascular congenital malformations in these cases (see Table IV) forces one to the conclusion that all these conditions probably have some common general etiological factor, and certainly in matter of time-relationship are obviously congenital.

4. In the twenty-six cases illustrating this deformity of the aorta when examined at necropsy, no instance was found where similar constriction had occurred in the pulmonary artery. If the peculiar tissue of the ductus produced constriction of the aorta in the cases cited in this paper, then it is a remarkable fact that constriction did not similarly take place in the pulmonary artery as the result of extension of the tissue into that artery.

5. In none of the cases here recorded was there evidence which would indicate that the lesion had been a progressive one. The degree of constriction was pronounced in subjects less than a week old.

6. The mechanism associated with the conversion of the foetal circulation into that of the newly-born appears to be adverse to a process which would involve a narrowing of the aortic lumen. At this transitional period the pressure within the ductus is lowered, and that within the aorta is raised. The former should facilitate the closure of the ductus, and the latter should help to produce dilatation rather than constriction of the aortic lumen.

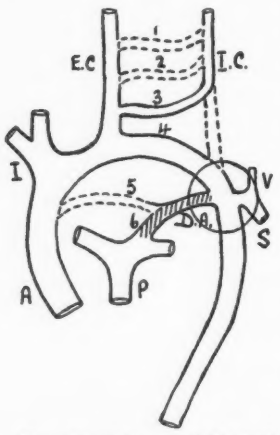

FIG. 18. Scheme of the left aortic arches and their developmental transformation, modified after Kollmann. Discontinuous lines indicate vestigial arches. Numerals indicate the six arches. (A) Aorta; (P) Pulmonary artery; (I) Innominate artery; (E.C.) and (I.C.) External and internal carotid arteries; (S) Left subclavian artery; (D.A.) Ductus arteriosus; (V) Left vertebral artery. Circle locates the site of deformity in cases grouped as Types I, II, III, and IV.

Each of these data supports the contention that the lesion is an example of developmental abnormality, yet it has not been possible to supply what must be regarded as the most potent argument in favour of such a view. No example of the deformity was found amongst 330 foetuses examined at necropsy. Although such a finding in the foetus would prove the congenital nature of the lesion, yet when it is considered that the incidence has been established as only one in a thousand, its absence in 330 foetuses does not bear much significance.

In the course of development six pairs of aortic arches are formed; the left arches are outlined in Fig. 18. The fourth left arch constitutes that portion of the aortic arch which lies between the origin of the left common carotid artery and the aortic termination of the ductus arteriosus. The fifth arch on each side disappears. The sixth left arch gives off the pulmonary arteries and forms the ductus arteriosus.

In twenty-two cases (Types I, II, III, and IV), the deformity occurred adjacent to a point where the fourth and sixth primitive arches meet the vestigial portion of the dorsal aorta. In the remaining six cases (Types V and VI) the deformity had taken place in the truncus arteriosus.

Diagnosis

Symptomatology. No one symptom, and no collection of symptoms, can be claimed to indicate with certainty the diagnosis of congenital stenosis of the aortic arch. In infants the exact nature of the lesion can only rarely be established; a tentative clinical diagnosis of 'congenital heart disease' is usually made, and examination at necropsy is necessary to reveal the actual anatomical deformity. It is also rare for any subjective symptom, occurring in an adult suffering from this condition, to direct attention to the initial

lesion which has caused the illness. Usually the presenting symptoms are those caused by some complication which has been superadded, so that some or all of the symptoms of heart failure, rupture of mycotic aneurysms, subacute bacteraemic endocarditis or cerebral haemorrhage, may be present. Other cases may have remained symptom-free and die from some intercurrent disease. Case 12, in which death was due to pulmonary embolism and carcinoma of the pylorus, is an example of this group where the degree of constriction in the aorta is not severe.

Although the symptomatology in many cases, therefore, may prove to be vague and of little value in directing attention to the exact nature of the lesion, the author believes that a symptom presented by Case 9 may prove peculiar to, or even pathognomonic of, the condition. This patient complained of numbness and weakness in both legs whenever he assumed an upright posture after reclining for some little time in the horizontal position. As he changed from the latter to the former posture he experienced a sensation of ' blood rushing back to the legs '. He stated that the sensation was comparable to the one he experienced when the pressure within the pneumatic bag of the sphygmomanometer placed around the thigh was released. These symptoms disappeared on walking a short distance and were never precipitated by the act of continued walking, although he had walked distances of twenty-five miles during a recent holiday. This patient has also noticed that if his feet ever become cold he finds it very difficult to get them warm again. In Case 18 there was no complaint of either of these symptoms, but recently the patient had experienced severe pain localized along the border of the left scapula. The site of the pain corresponds with the area where the hypertrophied arteries forming the collateral circulation are most prominent, and it is suggested that the pain may be caused by the erosion of ribs.

King (1926) referred to nocturnal frequency of micturition as a common symptom, but it was not found among the cases discussed here.

Although it has not been possible to discover any specific *subjective* symptom which may prove of great value in the diagnosis of congenital stenosis of the aortic arch, nevertheless, the recognition of a collection of *objective* symptoms makes it possible to diagnose with certainty those cases exhibiting this anomaly and included in Types II and III, and a short reference to each of these will now be made.

Heart signs. It is seldom if ever safe to rely on physical signs obtained from examination of the heart as indicating the diagnosis of this congenital lesion. The deformity is a vascular one, but owing to its proximity to the heart the latter does undergo certain changes which have been described in a previous section and which give rise to certain physical signs.

In those cases classified as Type I the signs indicate patency of the ductus arteriosus. A rough systolic murmur heard over the base of the heart has its site of maximal intensity in the pulmonary area. A systolic thrill may be present. The second sound in the pulmonary area is audible or accentuated.

The apex-beat is not displaced and enlargement of the right heart may not be detected on clinical examination.

In cases forming Types IV and V, signs indicating patency of the ductus arteriosus may occur, but owing to the uniformity of the vascular lumen connecting the pulmonary artery with the descending thoracic aorta, no murmur may be elicited. In this class cyanosis is a prominent feature and death occurs within a few days of birth.

Cases belonging to Type VI present no characteristic signs on examination of the heart. Here also cyanosis is a prominent feature and early death ensues.

Cases classified as Types II and III show hypertrophy of the left ventricle. The apex-beat, which is usually forcible, is displaced outwards. A basal systolic murmur is frequently audible. The aortic second sound is usually accentuated, sometimes duplicated, and occasionally obscured by a diastolic murmur. Aortic incompetence was present in three of the eleven cases which form Types II and III. In each of the three cases this was in the nature of 'relative incompetence', while in two of them bacteraemic endocarditis had supervened. Care must be taken to distinguish cardiac murmurs from those found over the hypertrophied arteries which form the collateral circulation.

When, therefore, other pathognomonic signs have indicated the diagnosis of congenital stenosis of the aortic arch, then the corroborative physical signs described above should be sought for in the examination of the heart.

Vascular signs. The recognition of tortuous and hypertrophied arteries in the neck, chest wall, back, and upper abdominal wall, representing the collateral circulation formed in cases of congenital stenosis of the aortic arch, is not new. Wernicke (1875) described the establishment in such cases of a system of anastomosis between the superior intercostal and the aortic intercostal arteries, between the transversalis colli and the aortic intercostal arteries, between the internal mammary arteries and the aortic intercostal and deep epigastric arteries, and between branches of the axillary and scapular arteries.

In this connexion the present investigation appears to emphasize that this system of collateral circulation can only become established in those cases where the ductus arteriosus has closed; but a possible exception to this rule has already been discussed. Thus it was a prominent feature in seven of the ten cases forming Types II and III. In the remaining three cases the fact that the degree of constriction of the aorta was not severe, and that all three subjects were young (three months, eighteen months, and six years respectively), explains the absence of a compensatory circulation in these instances.

The network of anastomotic vessels had not formed in any of the cases where congenital stenosis of the aortic arch was associated with patency of the ductus arteriosus. Therefore, while the presence of this arterial anastomosis in the upper part of the trunk may be held to indicate the diagnosis of congenital stenosis of the aortic arch, its absence does not negative

a similar diagnosis in a case which presents certain other features of the condition.

Blood-pressure readings. Discrepancy between the size of the radial and femoral pulses has long been known to occur in cases with stenosis of the distant portion of the aortic arch, and the recognition of this inequality has proved to be of great value in the diagnosis of the condition. The radial pulse is full and in some cases unequal on the two sides, while the femoral pulsation is often very difficult to elicit and scarcely perceptible to the examining finger. It is known (White, 1931) that the systolic blood-pressure in the femoral artery in the case of healthy subjects exceeds that in the brachial artery by 20 to 40 mm. of Hg. In those cases of congenital stenosis of the aortic arch where the ductus arteriosus has closed, the reverse is the rule, and the systolic blood-pressure reading in the arm is found to be considerably higher than in the thigh. The oscillometer may aid the measurement of pulse-fullness in a limb where there is restricted circulation, and the readings obtained in Case 9 from the use of Pachon's oscillometer prove instructive (Table III). In the same case the brachial blood-pressure registered by the sphygmomanometer proved to be 165/95 in the right arm, 155/95 in the left arm, and 145/– in the right thigh. In Case 18 the brachial blood-pressure was found to be 205/120, while the femoral registered 85/–.

Radial and femoral tracing. The distance between the heart and the radial artery at the wrist is greater than that between the heart and the commencement of the femoral artery, so that in normal subjects the femoral pulse precedes the radial by 0·01 to 0·02 seconds. In cases of congenital stenosis of the aortic arch, a comparison of the rate of pulse transmission in the radial and femoral arteries may indicate obstruction occurring at a point distant to the origin of the innominate or the left subclavian arteries. The radial and femoral tracings obtained in Case 9 (Fig. 8) showed the radial to precede the femoral by 0·01 seconds.

Radioscopy. Certain well-recognized changes may be detected in the heart, aorta, and ribs by X-ray examination of cases which present congenital stenosis of the aortic arch. These findings are in accordance with the changes already described and which disturb the anatomical outline of the heart and the aorta.

In those cases classified as Type I the outline of the heart shadow will be similar to that found in patency of the ductus arteriosus uncomplicated by congenital stenosis of the aortic arch. Thus there is prominence of the pulmonary arc and enlargement of the right auricle in the antero-posterior view and of the right ventricle in the left oblique position, and no enlargement of the left auricle in the right oblique position.

Those cases described as Types II and III present certain characteristic features. Thus, there is enlargement of the left ventricle, and the ascending aorta bulges prominently to the right and may show considerable dilatation, as in Hunter's (1928) case. The aortic knuckle, which represents the

terminal portion of the aortic arch and marks the seat of the constriction in these cases, may be small or absent. When examined in the right oblique position, the barium-filled oesophagus is seen situated to the right of the aortic arch as in the normal subject. These findings were present in Cases 9 and 18 (Plate 1, Fig. 7, and Plate 3, Fig. 12). Fray (1930), in an admirable paper reviewing the roentgenological diagnosis of stenosis of the aortic arch, has referred to a defect or break in the continuity of the aortic outline, which is best seen in the left oblique position. He stated that the indentation was usually more conspicuous on the convex side of the arch. It was not possible to confirm this finding in Cases 9 and 18. Presumably atheroma of the aorta in elderly subjects, or conspicuous dilatation of the aorta proximal to the site of stenosis giving rise to an increased column of blood, are findings that facilitate the discovery of this *gap* in the aortic shadow.

Meckel (1827) described a case where constriction of the aorta just below the ligamentum arteriosum led to death from rupture of the right auricle. The account of the case includes a diagram (Plate 2, Fig. 19) which demonstrates the course of the anastomosing vessels and illustrates erosion of some of the ribs. According to the diagram the eroded areas are shown at the upper border of the ribs. Walshe (1873) stated that 'occasionally a local expansile pulse, aneurysmal to the feel and sometimes strong enough to gradually wear away the ribs, may be felt from place to place in the intercostal vessels'. It would appear that Walshe's statement was based on Meckel's case. Erosion of the ribs by dilated and tortuous intercostal arteries in congenital stenosis of the aortic arch was first recognized in radiograms by Rösler (1928). Railsback and Dock (1929) reported a case where the aorta appeared to be normal on radiological examination, and where numerous erosions of the third to the ninth ribs had occurred, although the degree of superficial collateral circulation was small. Pezzi and Agostoni (1930) reported a case in which a radiogram of the thorax demonstrated erosion of the ribs. Blumgart, Lawrence, and Ernstene (1931) similarly demonstrated erosion of the ribs in two cases. Fig. 1 in Hamilton and Abbott's (1928) paper also illustrates the same localized destruction occurring along the lower border of several ribs. Similar destruction is shown in East's (1932) case. Radiograms from unpublished cases illustrating the same changes have been shown to me by Dr. John Parkinson and Dr. D. Evan Bedford. In teleradiograms of Cases 9 and 18 (Plate 1, Fig. 7, and Plate 3, Fig. 12), several small areas of focal erosion are seen at the lower border of the ribs in their posterior portions, and reaching forward in the case of one rib to the posterior axillary line. The anterior portions of the ribs appeared intact, and so far no case has been published where the anastomotic vessels formed adjacent to the internal mammary artery have produced local destruction of the rib margin at this site. The internal mammary arteries themselves do not produce this radiological sign, because they rest on the cartilaginous portion of the rib.

A Short Note on Prognosis and Manner of Death

In a case of congenital stenosis of the aortic arch, prognosis is uncertain. Many die in infancy, while in those cases which survive adult life the complications associated with the condition are such as to prevent the expression of hopefulness in estimating the probable duration of life. It is true that a few cases have lived to old age. Other authors, Fraenckel (1912), Kolisko (1913), Meixner (1922), and Strassman (1922), have stressed the importance of trying to assess the probable longevity of cases in medico-legal work. Case 9 serves as an example to emphasize the necessity of taking precaution in symptom-free applicants for a life insurance policy where there is found a raised blood-pressure, excessive pulsation in the neck, a forcible apex-beat, and an obscure cardiac murmur.

Although the degree of stenosis does not in itself determine the prognosis in a given case (Case 19, in whom there was atresia of the aortic arch, lived to the age of 32 years) it may be held as a safe generalization that the greater the degree of stenosis the greater is the liability to complications, and so the more grave becomes the outlook. In many cases, therefore, it will often be important to attempt to estimate the degree of stenosis present. It is not possible to do this in those cases where patency of the ductus arteriosus persists, and this test can only be applied in a speculative way to those cases included in Types II and III. The following are four desiderata that may help to determine the degree of stenosis present: 1. The extent to which the system of collateral circulation has been established. 2. The absence of the aortic knuckle to the left and the prominence of the ascending aorta to the right, as determined by radioscopy. 3. The degree of hypertrophy of the left ventricle. 4. Erosion of the ribs may occur with minor degrees of stenosis, but, when this is a prominent feature, the inference that the obstruction is a pronounced one is justifiable.

TABLE V

Showing the Cause of Death in 26 Cases of Congenital Stenosis of the Aortic Arch discussed in this Paper

Cause of death.	Number of cases.	Average age.
Heart failure	13	2 years, 11 months
Broncho-pneumonia	4	4 years
Bacteraemic endocarditis	2	27 years, 6 months
Rupture of mycotic or false aneurysm	3	26 years
Congenital stenosis of intestine	2	6 days
Pulmonary embolism	1	60 years
Foreign body in bronchus	1	1 year, 6 months

The frequent occurrence of infection in the walls of abnormal arteries associated with this condition influences the prognosis unfavourably. Infection of the arterial wall leads to aneurysmal dilatation, and rupture is not an uncommon complication. It is significant that the cause of death in three of the twenty-six cases was rupture of a mycotic aneurysm in two

and of a false aneurysm in a third case. The aneurysm in two cases had occurred in the aorta proximal to the seat of the constriction, and in the third instance had formed in the aortic portion of the ductus arteriosus. It is not intended in this paper to review the causes of death in all the published cases of congenital stenosis of the aortic arch, as this has been admirably carried out by Abbott (1928), who analysed the cause of death in 200 cases collected from the literature. Of these, seventy-seven had died from heart failure; rupture of the aorta had caused death in thirty-eight, and rupture of the heart in two cases. A cerebral lesion had occurred in twenty-six instances.

Summary

A study has been made of twenty-eight cases of congenital stenosis, atresia, or interruption of the aortic arch; twenty-six cases had been examined at necropsy. The incidence of these congenital anomalies among subjects examined at necropsy was found to be approximately one in a thousand. The average age in the present series was 11·4 years, and when the ratio of males and females examined at necropsy was considered it was found that the condition had only a slightly higher incidence in the male. It was found possible to separate the cases into definite types according to the anatomical features present. It is claimed that the recognition of such a classification will, firstly, facilitate the more ready interpretation of the clinical findings and appearances elicited by radioscopy of the heart and aorta, and, secondly, will obviate the necessity of propounding two or more theories to explain the pathogenesis of what have been regarded in this paper as anatomical varieties resulting from a common process. The features that characterize each of the six types are outlined, and a short description of the cases is appended in each group. Patients living beyond early infancy are found in Types I, II, and III only; few in Type I with the ductus patent; more in Types II and III with the ductus closed. Other developmental abnormalities that may accompany this congenital deformity of the aortic arch are enumerated. The diagnosis of the condition is discussed with special reference to symptoms, heart signs, vascular signs, blood-pressure readings, radial and femoral tracings, and radioscopy. A short note has been added on the prognosis and manner of death in patients presenting this congenital anomaly.

It is a real pleasure to acknowledge once more my indebtedness to Professor Hubert M. Turnbull for placing unreservedly at my disposal the records and material in the Bernhard Baron Institute of Pathology and for his helpful suggestions and criticism. I wish also to thank Dr. W. W. Woods and Dr. A. B. Bratton, who have been responsible for recording the findings at necropsy in many of the cases included in this paper. I am exceedingly grateful to Mr. E. P. Stibbe for reading my paper and giving me the benefit

of his special knowledge of the subject. I wish to thank Dr. E. C. Daniel, of Epsom, for having kindly referred Case 9 to me. From my chief, Dr. John Parkinson, I have had help in the radiological diagnosis.

The work has been done working under the tenure of the Paterson Bequest.

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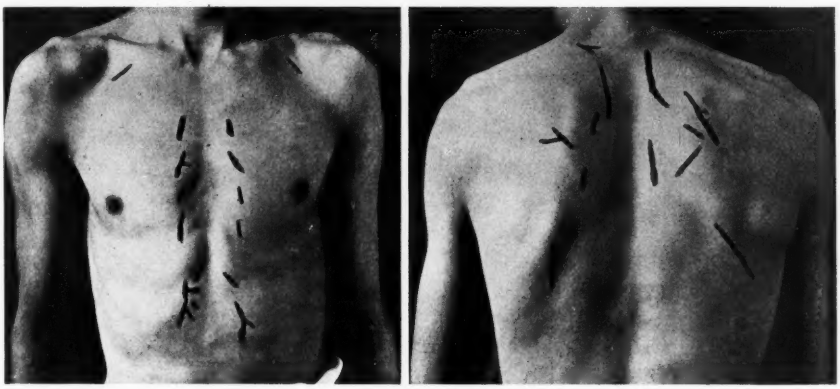

FIGS. 4 and 5. Illustrating the site and distribution of the hypertrophied arteries forming the collateral circulation in Case 9

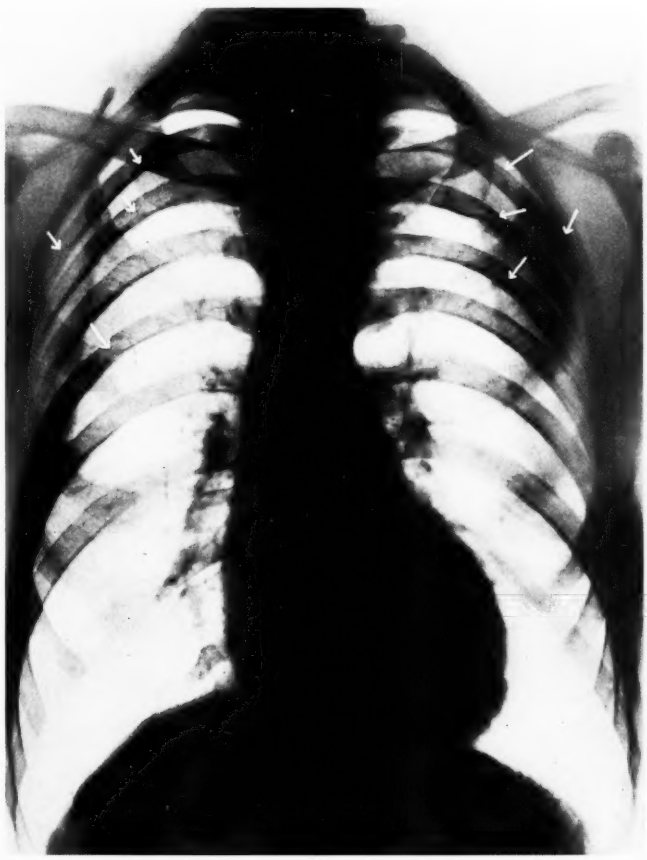

FIG. 7. Teleradiogram in Case 9. The arrows indicate focal areas of erosion in ribs

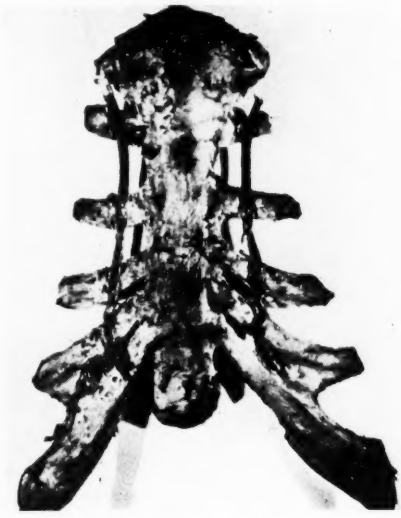

FIG. 9. Showing the hypertrophied internal mammary arteries in Case 17

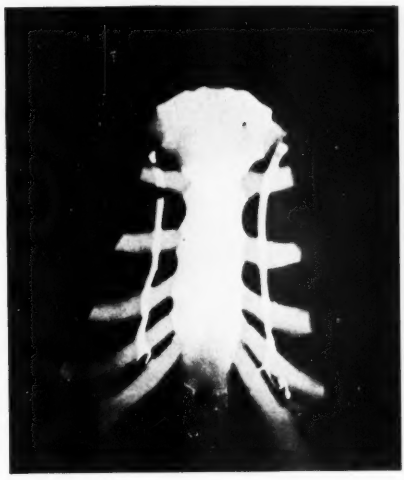

FIG. 10. X-ray photograph of the barium-filled internal mammary arteries in Case 17

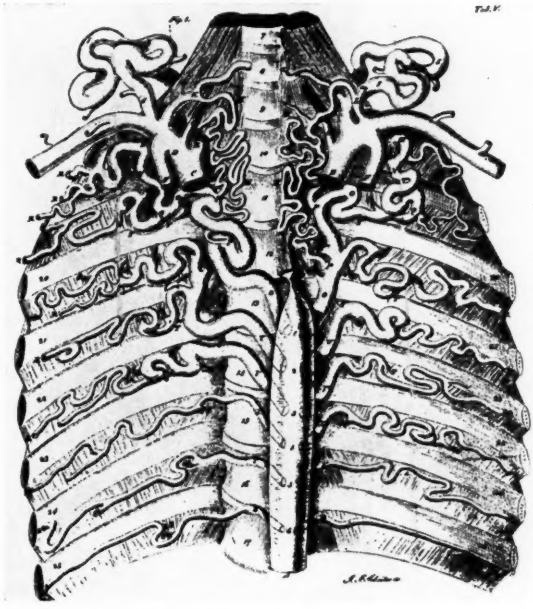

FIG. 19. Diagram showing the arterial anastomosis formed in Meckel's case. The drawing also depicts erosion of the upper borders of some of the ribs

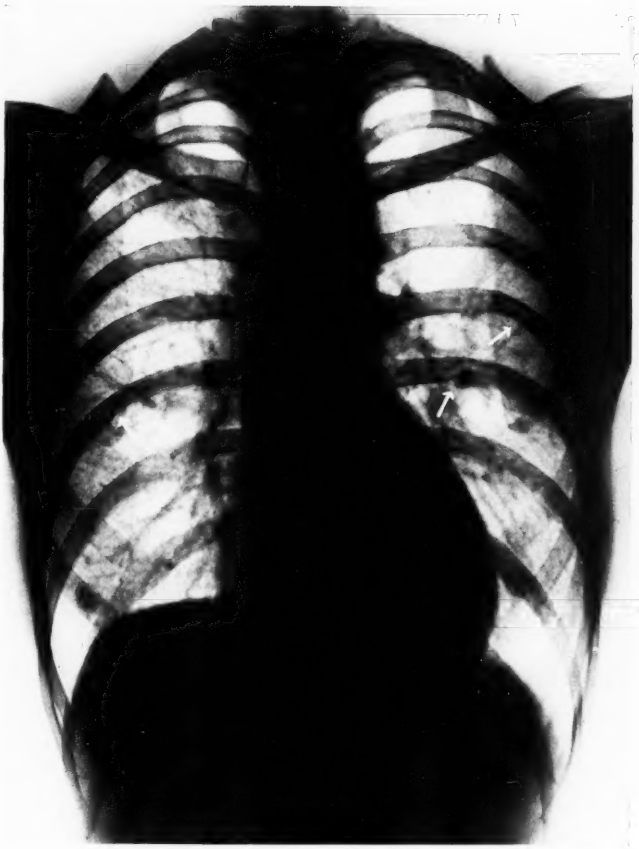

FIG. 12. Teleradiogram in Case 18, showing enlargement of left ventricle, small aortic knuckle, prominence of ascending aorta and erosion of ribs

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THE THERAPEUTIC USE OF DRUGS OF THE DIGITALIS GROUP[1]

By ELSIE PORTER

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With Plates 4 to 8

In this investigation of some drugs of the digitalis group the following problems have been considered: (1) The effect of massive digitalis dosage when given by the mouth or by the rectum. (2) The value of massive doses of strophanthin given intravenously. (3) The relative potency of the various preparations and methods used. (4) The place of action of this group of drugs.

1. *Massive Digitalis Dosage by Mouth*

All the cases studied in this paper were suffering from auricular fibrillation, because graphic records are easily obtained and easily read and the effects of the drug easily perceived in the slowing of the pulse. The introduction of Eggleston's massive method of digitalis administration (2) enables reliable pharmacological experiments to be completed within a stated period of ten to twenty hours.

In the previous work done on this subject when the dose is spread over several days, it must be noted that other factors come into play, such as rest in bed and nursing. These alone, without the administration of any drug, cause a certain slowing of the heart's action. The method adopted in these investigations was the same as that originated by Eggleston, with the modification that a fully calculated massive dose was given in a single draught instead of in several portions spread over one or two days. This required the patient to be free from the action of drugs of this group at the time of investigation; moreover, the dose of the particular drug that would yield the full therapeutic, though no toxic effect, must be calculated as accurately as possible.

In all cases, therefore, a careful inquiry was made to ensure that the patient had not been taking any drug of the digitalis group during the preceding three weeks. According to Eggleston and others, a full therapeutic effect of a good standard tincture may be calculated at the rate of 0·146 c.c. per pound body-weight of patient (1). This dose, in our cases, was found almost always to produce vomiting. Withering, indeed, stated

[1] Received June 22, 1932.

'that the use of digitalis has only been given a fair trial when administered to the point of production of one or more criteria of minor intoxication, and to obtain the best results the dose should be just short of a toxic dose'. The dose used, therefore, was reduced until adequate slowing was produced without vomiting.

Standardization. The introduction of an international standard powdered leaf has helped greatly in the pharmacological standardization of drugs of the digitalis group.

The tincture of digitalis used in this investigation was prepared so as to ensure that the potency was represented by 100 per cent. as compared with the international standard tincture.

The method of standardization used is described in the *Pharmaceutical Journal*, vol. 117, p. 439 (1926).

The potency of the strophanthin used was such that 1 mg. of strophanthin was equivalent to 0·4 mg. of anhydrous ouabain.

Description of experiment. Of the patients with auricular fibrillation under supervision in the clinic, those who showed signs of congestive failure with high pulse speed were taken into the ward for treatment and study. They were all treated with the same tincture of digitalis to ensure that no variation in potency occurred. This point had been established by a long series of experiments in which varying doses had been used and their clinical and toxic effects noted.

The patient was first weighed and the dose calculated; no allowance was made for oedema or obesity. An electrocardiogram was taken and the patient then returned to bed. The draught was administered and eight hours later another cardiogram was taken. The photographs were then analysed to note the rate before and after digitalis, and any change in the cardiographic complexes.

By these means experimental conditions were fulfilled beyond that usually possible in clinical inquiry because the time of administration of the drug, the duration of its action, and the nature of the changes induced, could all be precisely determined and recorded. The maximum period of the experiment was eight hours, which excluded most of the effects from adventitious factors.

In the electrocardiographic record of this work, the necessity for showing the T-wave to the best advantage was important, as its inversion is one of the earliest toxic signs in the administration of digitalis and precedes vomiting. This wave has the greatest value in Lead II (right arm to left leg); Lead II is, therefore, recorded unless expressly stated otherwise.

The following table (Table I) shows the effects which were produced by the administration by mouth of a calculated dose of tincture of digitalis.

It will be noted that the doses which were calculated at the rate of 0·125 c.c. per pound body-weight gave the most satisfactory results. The 0·15 c.c. rate was found to be rather too high, and caused vomiting in some cases; while the 0·1 c.c. rate did not always produce adequate slowing.

Since this work was originally undertaken, the 0·125 c.c. rate has been adopted as the routine for massive doses and has proved the most satisfactory.

TABLE I

Cases of Auricular Fibrillation showing Ventricular Speed Before and Eight Hours After Massive Digitalis Dosage by Mouth

Case No.	Age.	Sex.	Before digitalis.	After digitalis.	'T' before.	'T' after.	Rate per pound.	Dose.
3	32	F	144	120	+	+	0·1 c.c.	10·2 c.c.
4	60	M	132	108	+	+	0·1 c.c.	15·6 c.c.
5	56	M	108	75	+	+	0·1 c.c.	13·4 c.c.
6	35	M	72	96	+	—	0·1 c.c.	13·6 c.c.
15	33	M	108	96	—	—	0·125 c.c.	12·0 c.c.
20	57	M	144	84	+	±	0·15 c.c.	15·0 c.c.
2	16	M	120	84	+	±	0·1 c.c.	14·5 c.c.
8	52	F	132	96	+	—	0·1 c.c.	11·0 c.c.
9	56	F	144	108	−2	−5	0·1 c.c.	18·2 c.c.
10	56	M	144	90	+	+	0·1 c.c.	11·2 c.c.
12	64	F	96	72	+	—	0·1 c.c.	17·3 c.c.
(*a*) 13	40	F	108	108	−2	−2	0·1 c.c.	13·0 c.c.
14	62	F	108	96	+	±	0·1 c.c.	11·3 c.c.
16	39	M	132	72	−3	−3	0·125 c.c.	18·5 c.c.
17	30	F	108	84	+	+	0·125 c.c.	12·7 c.c.
18	41	M	120	108	—	—	0·1 c.c.	15·3 c.c.
19	45	M	120	84	+	+	0·15 c.c.	21·7 c.c.
(*b*) 21	36	F	168	96	+	±	0·15 c.c.	36·5 c.c.

(*a*) Under continuous digitalis for two months prior to dose.
(*b*) Vomited four times after digitalis.

TABLE II

Cases of Auricular Fibrillation showing only Slight Slowing after Massive Digitalis Dosage

Case No.	Age.	Sex.	Before digitalis.	After digitalis.	'T' before.	'T' after.	Rate per pound.	Dose.
1	25	M	156	144	−5	−3	0·1 c.c.	13·2 c.c.
* 7	59	F	144	144	−2	−2	0·1 c.c.	17·7 c.c.
11	58	M	180	156	−1	−1	0·1 c.c.	16·8 c.c.

* Died fourteen days later.
Cases 1 and 11 suffered from severe myocardial damage.

Table II records three cases of auricular fibrillation which failed entirely to respond to digitalis therapy. One of these patients died fourteen days later, and the other two suffered from severe myocardial damage.

Clinical Effect

From the clinical standpoint this method of treating congestive cardiac failure has much to recommend it, in that the patient is so rapidly improved. One specific and striking example is as follows:

Male, aged 56 years, suffering from severe auricular fibrillation, was admitted to hospital at 6 p.m. with grave dyspnoea, difficulty in speaking, gross oedema, and with liver enlarged to the level of the umbilicus. His cardiogram showed a ventricular rate of 180; he was accordingly given

a massive dose of digitalis at 10 p.m. The next morning at 10 a.m. he was found reclining comfortably in bed with a pulse-rate of 90, no dyspnoea, able to proclaim his improvement, the liver and oedema much reduced, and he was reading his own bed chart!

It follows from Table I that a full therapeutic dose must be carefully calculated for a particular tincture if it is to avoid any toxic effect. Any change in the tincture used will probably require some slight alteration in the calculated rate. During the latter part of this work the same tincture has always been used. This has been found to give quite satisfactory results, both from the point of view of the degree of slowing of the cardiac rate and of the absence of toxic effects, such as severe vomiting, when calculated at the rate of 0·125 c.c. per pound body-weight.

The writer believes that a single massive dose is not only safe, but is the method of choice, on account of its rapidity of action, precision of effect, and duration of benefit. The problem is only partly solved, however, because, out of fifty consecutive cases of auricular fibrillation which were admitted to hospital with congestive failure, twenty-two have suffered from vomiting, although they were free from digitalization. As Eggleston says: 'To complicate the question of the absorption of the digitalis bodies from the alimentary canal of man, and hence to complicate that of dose, we have often to deal with cases of cardiac failure in which dilatation of the heart has resulted in splanchnic congestion and vomiting when the patients come under treatment' (3).

The next step appeared to be, therefore, to find some other route for the administration of adequately calculated doses of this group of drugs, which would enable us to restore the cardiac balance with the same therapeutic certainty as could be obtained by mouth in the absence of vomiting. Congestive cardiac failure with its anasarca, cyanosis, and orthopnoea, is sufficiently distressing in itself, but appears so much more dreadful when severe vomiting is added to the patient's other miseries. Any method which will avoid the latter contingency must of necessity prove a great boon to the patient.

The administration of the tincture of strophanthus by mouth was considered, in common with other investigators, to be too toxic, and too uncertain in its effects, although its smaller dose might have been a recommendation. Strophanthin given by some injection method, however, offered a better prospect. Here the first difficulty encountered was one of dosage, for, although the recommended dose of the tincture of digitalis varies from 2 to 30 minims thrice daily, and the 'larger dose in this instance is more than twelve times the smaller, this divergence pales into insignificance when compared with that encountered in the case of strophanthus or strophanthin', which Hatcher and Bailey reported from the literature. They found that the largest daily dose used was some 750 times as great, in terms of activity, as the smallest single dose recognized by authorities (3).

Such being the case, it seemed almost impossible either to decide the

dose, or risk the wide variation in absorption, a point showing a quite unusual amount of agreement amongst authorities.

Two further methods appeared to offer some promise, either by some form of injection subcutaneously or intravenously, or by the rectal route.

Injection Method

Intravenous strophanthin. At the time of the investigation it was impossible to discover sufficient evidence to guide us in the estimation of a correct massive dose, and no evidence whatever to guide us as to a means for calculating it.

Cornwall (5) recommended doses of 1/1000 to 1/500 gr., three to six times daily, the former dose being safely continued indefinitely in daily doses. Doses of 1/250 gr. could be administered four-hourly only for a short time, and doses of 1/100 gr. could only be given once in twenty-four hours. The method of administration recommended was ordinarily intramuscularly, sublingually, and hypodermically, and only in emergencies, such as myocardial insufficiency, was the drug to be given intravenously.

Grünbaum (6) considers that in all cases in which digitalis effects an improvement strophanthin is equally effective. He recommends a single intravenous dose of 1/130 gr. provided there has been no digitalis therapy for forty-eight hours previously. This is better given divided into two doses of 1/260 gr., night and morning of the same day. The initial dose can be repeated daily, or every other day, till the therapeutic effect is obtained.

von Hoesslin (7) recommends therapeutic doses of 1/130 gr. (0·5 mg.) up to 1/60 gr., to be given in divided doses. He considers that the drug should be used with great caution, owing to its toxic effect and the liability to sudden death, and reports cases of sudden death after doses ranging from 1/130 to 1/20 gr.

In the hypodermic administration of any drug, there is always the problem of the time occupied in the absorption of the drug as well as the uniformity of the rate of absorption. As it was determined to employ a graphic method of recording results, it was imperative to know clearly that the drug was absorbed completely, and to know also the precise time of its action. The problem was further complicated by the oedema and passive congestion from which these patients usually suffered. In these cases the return of the blood to the right side of the heart is considerably delayed, and in consequence there would be the likelihood of delay in the absorption of the drug.

For this reason, and because of the gravity of the illness in question, the employment of the intravenous route appeared to be not only fully justified, but eminently desirable. Furthermore, it yielded an opportunity for making more precise and accurate records. Prior to the administration of

the strophanthin, the same precautions were taken as before with regard to the freedom from action of any drugs of the digitalis group.

Preparation used and dosage. The same preparation was used throughout the whole series of cases. This preparation was supplied by the great kindness of Dr. J. H. Burn of the Pharmaceutical Society's Laboratories, London. It was in tablet form, each tablet containing 1/100 gr. of strophanthin.

In view of our ignorance of a suitable dose, and of the length of time which would be taken before any response was obtained, a few preliminary observations were made with doses of 1/100 gr. Unfortunately, no effect whatever could be observed with these doses, and there was no slowing of the cardiac rate. The dose was then raised to 1/50 gr. and, with this, a certain degree of slowing was obtained without any untoward effect. The ultimate result, however, was far from being so satisfactory as that to which we were accustomed, after a massive dose of this drug by mouth. The dose was accordingly again raised to 1/33 gr. (three tablets in one c.c. of distilled water) and the following technique was observed.

The patient was placed in the cardiographic circuit, and a preliminary tracing was taken. The needle was then inserted in the vein of the left arm, making sure that it was so by withdrawing a little of the blood back into the syringe, and the tracing was continued. A mark was then made on the paper showing the moment the drug had completely entered the vein. Tracings were then repeated at five-minute intervals for half an hour, the time being recorded by a stop-watch set going at the moment the drug entered the vein.

By this technique it was found that a full therapeutic effect was apparently obtained in half an hour, for by this time an efficient grade of slowing had taken place in most cases. See Plate 6.

The work of other investigators agrees with these findings in this respect, for von Hoesslin (7) found that the effect of an intravenous injection began to show itself in two minutes, and that the maximum effect was reached in twenty minutes. He also records cases of sudden death after injection of doses ranging from 1/130 to 1/20 gr., and in all cases the deaths occurred between twenty to forty minutes after the injection. Very rarely has poisoning taken effect in two to three hours later, and it is doubtful if it ever happens later than this period.

In experiments on animals, the findings were similar. Fühner (8) found, in the perfusion method with frogs, that the time of poisoning was ten to twenty minutes after injection, and Mancke (9) found that experimental lethal effects in animals could be expected in twenty-five minutes.

It is, however, tenable, as before mentioned, that the maximum therapeutic effect of the strophanthin, as with digitalis, has not been attained without the establishment of some grade of vomiting. The dose was therefore again raised to 1/25 gr., to see if a better result could be obtained. This dose, however, appeared to be quite definitely toxic in its effect, and in

one case, at least, the effect of the drug, as shown by the electrocardiographic record, was of such toxicity as to be distinctly alarming. (See Plates 4 and 5.)

It may be appropriate to say here that toxic effects from the administration of massive doses of drugs of the digitalis group, apart from mild grades of vomiting, inversion of the T-wave in the cardiogram, and coupling of the beats, are in our experience distinctly rare. There appear, however, to be two groups of cases in which these symptoms presented themselves on occasions.

1. Cases known as spasmodic fibrillation, in which the change from normal rhythm to a high-speed fibrillation occurs with the same suddenness, and possibly from the same causes, as the change from normal to abnormal rhythm in cases of paroxysmal tachycardia.

2. Cases in which the form of their cardiograms already indicates a considerable grade of myocardial damage. The fact, however, remains that in our experience of something over 300 cases of auricular fibrillation who have been treated by this group of drugs in various ways, there have been only four cases showing these alarming toxic effects.

In Table III the results obtained in some of the experiments are set out, and an analysis of the effects obtained with different doses of strophanthin.

Notes: Case 15 was apparently a case of spasmodic fibrillation, found not to be fibrillating at the beginning of the injection. The heart went into delirium cordis and fibrillation after injection. The patient developed a cerebral embolism on the following day and died.

Case 2. A case of spasmodic fibrillation—not fibrillating at the time of injection. Was fibrillating two days later, and remained so until death nine days later.

Of the cases in which intravenous strophanthin was given, in one case given 1/50 gr. the maximum slowing in 30 minutes was from 120 to 114. There was no vomiting, no extra-systoles, and the T-wave was not inverted. Eleven cases were given 1/33 gr.; the average amount of slowing was 45·6 beats per minute. Vomiting occurred in one case, in which the patient had been taking 70 minims daily of the Roche tincture of digitalis for the three days preceding the experiment, but none prior to this. Extra-systoles were noticed in five cases. One of these was the patient quoted above. Another was a case of apparent spasmodic fibrillation who, at the time of administration of the drug, was found to be regular, but who went into delirium cordis and fibrillation after the injection of the drug, and developed a cerebral embolism followed by death. In seven cases the T-wave was unaffected. In three it was inverted in thirty minutes. The result of this dose was good; there was adequate slowing and few toxic effects. Five cases were given a dose of 1/25 gr. There was an average slowing of 48 beats per minute. In this average is included one case which slowed from 96 to 84. This case was one of spasmodic fibrillation—but not fibrillating at the time of injection; fibrillation occurred during the injection, and remained so until death, which occurred nine days later. Excluding this case, the average rate of slowing was 56·4 beats per minute. Vomiting occurred in one patient at thirty

TABLE III. *Intravenous Strophanthin*

Number.	Age.	Sex.	Dose in grains.	Rate before.	Rate after 5 minutes.	10 minutes.	15 minutes.	20 minutes.	25 minutes.	30 minutes.	'T' before.	'T' after.	Vomiting.	Remarks.
1	54	F	1/33	144	144	132	120	84	96	96	+	+	nil	Three extra-systoles
2	18	F	1/33	120	120	120	108	96	108	96	+	+	nil	Spasmodic fibrillation. One extra-systole
3	49	M	1/33	108	96	72	72	72	60	60	+	—	nil	No extra-systole
4	58	M	1/33	121	144	96	84	96	96	96	+	+	nil	No extra-systole
5	49	M	1/33	180	144	108	108	108	108	108	+	+	nil	No extra-systole
6	53	M	1/33	120	108	96	84	84	60	72	+	+	nil	One extra-systole
7	58	M	1/33	180	120	108 coup.	96 coup.	84 coup.	120 coup.	0	±	±	at 23 mins.	Frequent extra-systoles. Had taken 70 minims tinct. digitalis Roche during three days previously
8	69	F	1/33	120	108	84	84	72	84	72	+	—	nil	Frequent extra-systoles
9	46	F	1/25	108	72	72	72	60	60	60	+	—	nil	No extra-systole
10	51	F	1/25	156	96	120	72	72	72	72	—	—	nausea only	Very toxic symptoms. Frequent extra-systoles
11	57	F	1/25	144	84	84	84	72	72	84	—	—	at 30 mins.	Vomited once daily for three days
12	37	M	1/25	108	60	60	72	60	60	60	+	+ reduced in size	nausea only	No extra-systoles
13	44	M	1/25	144	120	144	156	120	108	108	—	—	nausea only	No extra-systoles
14	49	F	1/33	168	156	132	120	96	96	132	+	+	nil	Nil
15	50	F	1/25	96	120	84	84	84	84	84	no record		nil	Cerebral embolism following day; death
16	35	F	1/50	120	144	114	114	114	114	120	+	+	nil	No extra-systoles
17	40	F	1/33	156	84	78	66	72	66	72	no record		nil	No extra-systoles

minutes, and thereafter once daily for three days. There was nausea in three cases. Frequent extra-systoles and very toxic symptoms occurred in one case. The T-wave was unchanged—though in three cases it was inverted at the beginning, and in one case the upward wave was reduced in amplitude. As a result of this dose adequate slowing was obtained, but it was considered too toxic.

The conclusions to be drawn from the foregoing are that, provided the patient has not received any drug of the digitalis group for an adequate period prior to the administration of the strophanthin, the intravenous route affords a very satisfactory method, and that a dose of 1/33 gr. represents an adequate massive dose from which the same type of result may be confidently anticipated as from the oral method of administration. The effect of the drug can be observed at the end of thirty minutes, as against the eight hours occupied in gastric absorption.

It will be noted, in this series, that no calculation is made for body-weight. Such cases as were treated were all of average weight, and it was considered that a very much larger series of experiments would be necessary to recast the results involving any such calculation, in view of the form in which the drug is usually issued to the public. On the other hand, Grünbaum (6) considers that the capability of precise dosage of strophanthin is greater than with digitalis preparations. One is forced to the conclusion that the preparations used in Germany differ from those used here.

It may be noted in passing, that even in a large cardiac clinic it is not easy to find a sufficient number of patients who require this form of treatment, and who arrive at the hospital without having had some form of digitalis already administered to them. Even Eggleston admits the same difficulty.

It is felt, in justification of this method of administering intravenous strophanthin, that what it may lack in precise accuracy of dosage is fully compensated for in the rapidity of action and certainty of effect, and this even when congestive vomiting is frequent.

Administration of Digitalis per Rectum

Two cases had been treated by this method a few years ago, but the results were so poor that the work had been abandoned. In view of later work it was thought that the selected cases had been unsuitable, as both were oedematous and practically *in extremis* and their powers of absorption by then were probably nil. The dose given was in all probability too small in any case.

As a means of estimating the dosage, experiments were then made on a series of cases. On the assumption that probably a larger dose would be required than the 0·125 c.c. per lb. body-weight as for the oral route, the first doses were calculated at the 0·150 rate, and even this was exceeded in some cases. One case received 21 c.c. when the calculated dose should have been

13 c.c. at the 0·125 c.c. per lb. rate; another case received 21 c.c. when the calculated dose should have been 18·2 c.c. In the former case vomiting occurred five and a half hours later, but there was no vomiting in the second case. The T-wave in Lead II was inverted in both cases.

Another case was given a dose calculated at the 0·150 rate, and this patient vomited three hours following the dose. Five cases were then given doses calculated at the 0·125 rate. Of these, one case had severe vomiting. This case was one of hyperpiesia who died the following day. One case vomited twice, nine and fourteen hours later. In one case there was nausea only, and in two cases there was no vomiting. The T-wave was inverted in two cases. Adequate slowing was obtained in all cases.

Method. A simple enema was given six hours prior to the dose in order to prepare the bowel for absorption. The digitalis was then diluted up to three ounces with water, latterly with normal saline, and was administered slowly with tube and funnel at body temperature. On the whole it was well retained by the patients. A cardiogram was taken before the dose, whenever possible, and again six or eight hours later, the patient being kept in bed.

Proof of action. There was quite sufficient proof that the digitalis was completely absorbed, for the cardiac rate was slowed considerably, i.e. with an average of 48 beats per minute, and the T-wave was inverted in four out of five recorded cases. There was vomiting in five cases, severe in one, and nausea in one case. This occurred in three to nine hours after the dose.

The time taken to obtain a full therapeutic effect of the digitalis per rectum, as compared with that taken when administered by mouth, did appear to be slightly longer, but not appreciably so. Where a full therapeutic effect by mouth could be obtained in from four to six hours, the time occupied per rectum was about six to eight hours. On the whole it was considered that the 0·150 rate of dosage was too toxic, the 0·125 rate slightly higher than was necessary, and that probably the most satisfactory rate of dosage was that of 0·1 c.c. per pound body-weight. The following Table IV is an analysis of some of the cases treated.

Site of Action of Digitalis

It has long been known that atropin has the power of paralysing the vagus (vagal release), and that it produces in consequence a rise in pulse speed. As Lewis says (10): 'The conclusion that digitalis slows the ventricle by producing block in fibrillation is now generally accepted, but the precise manner in which block is induced is still disputed. Mackenzie held it to be vagal and Cushny to a direct action on the muscle. The discussion turns largely upon the reaction of the digitalized heart to atropin. The dose of atropin usually given to patients as a test, i.e. 1/50 gr., is hardly sufficient, or actually insufficient, to paralyse the vagi completely. Usually such a dose puts the vagus almost, but not entirely, out of action; to produce absolute paralysis

Table IV

Rectal Digitalis

No.	Age.	Sex.	Dose.	Rate per pound.	Speed before.	Speed hrs. after.		'T' before.	'T' after.	Vomiting.	Remarks.
1	58	F	23 c.c.	0·125	132	6	72	+	—	frequent	Hyperpiesia. Death on following day
2	56	M	20·5 c.c.	0·125	132	6	84	+	—	nausea only	
3	70	M	19 c.c.	0·150	132	6	72	—	—	3 hours later	
4	35	F	21 c.c.	calc. dose at 0·125 13 c.c.	132	5	60	+	—	5½ hours later	
5	34	M	21 c.c.	calc. dose 18·2 c.c.	132	12	84	+	—	nil.	Spasmodic fibrillation. Regular day following Greatly improved
6	43	M	19 c.c.	0·125	180	4	?	?	—	nil.	Embolectomy right arm, same evening; removed. Good result
7	52	F	21 c.c.	0·125	130	16	100	no record		occasionally and nausea	
8	53	F	16 c.c.	0·125	140	7	110	no record		9 and 14 hours later	Given 1/50 grain atropin prior to digitalis. Death following day
9	22	M	13·6 c.c.	0·125	98	12	84	no record		nil.	No cardiograms done

doses of 1/10 or 1/5 gr. are probably necessary, and preferably the dose should be intravenous. Such doses cannot always be given with impunity.' The customary dose of 1/50 gr. hypodermically, in this work, was found in conjunction with Lewis to be inadequate to produce a full vagal effect, but a dose of 1/25 gr. given intravenously, although causing some discomfort, such as vertigo, dry mouth, dilatation of the pupils, etc., produced no other serious effects, and in the majority of cases gave satisfactory vagal release, with an onset in point of time which can be clearly recognized.

Of digitalis by mouth. In this experimental work the patients, as before, were free from digitalis medication for three to four weeks. They were then given 1/25 gr. of atropin intravenously, and a continuous electrocardiogram was taken to show the rate before injection, and the rates during the two minutes following the injection. They were then given a calculated massive dose of tincture of digitalis by mouth, and six to eight hours later they were again cardiographed and at the same time given another dose of 1/25 gr. of atropin intravenously. An example of the type of result obtained is shown in Plate 8.

Of the twenty-one cases of auricular fibrillation studied, complete return to pre-digitalis release was obtained in 30 per cent. of cases, and considerable release in 60 per cent. of cases. Complete release was also obtained in cases after prolonged digitalization. The maximum release occurred (*a*) before digitalis, on an average at 46 seconds after the complete atropin injection; (*b*) after digitalis, on an average 49 seconds after injection. The earliest release was obtained 15 seconds after injection, and the latest after 60 seconds. The average moment of release before digitalis was 31 seconds after the injection of atropin, and 33 seconds after the administration of digitalis. Vagal release, then, can be obtained in 30 seconds from the moment of termination of the injection of atropin. It can be expected with certainty, and is therefore easily recognized and can be recorded graphically. It provides a highly satisfactory method of applying the test. Complete release shows that the whole of the digitalis effect is undoubtedly vagal, and where the release is incomplete the effect is largely vagal. It is believed that if and when a larger dose of atropin can be safely given intravenously the whole digitalis effect will be found to fall upon the vagus.

Of intravenous strophanthin. An attempt was made, by means of the above method of atropin release, to ascertain whether the site of action of intravenous strophanthin was the same as that of digitalis by mouth. One patient who had received an injection of 1/25 gr. of strophanthin two days previously was released with 1/50 gr. of atropin intravenously. The rate before the injection of atropin was 96, and in 45 seconds it rose to 144. Unfortunately there is no record in this case to show the degree of release before strophanthin therapy. Another case gave a more satisfactory answer. This patient had been digitalis-free for one month, and was given 1/33 gr. of atropin intravenously and cardiographed as before for two minutes. The ventricular speed rose from 132 per minute before the injec-

tion to 180 per minute 30 seconds after the injection. The following day 1/33 gr. of strophanthin intravenously reduced the ventricular speed from 132 to 84 in half an hour. Two hours later another dose of 1/33 gr. of atropin was given intravenously, and the ventricular speed again rose to 180 in 70 seconds. This case showed a complete release.

Of digitalis per rectum. Two cases were then studied which had received a massive dose of digitalis per rectum. In the first, the rate before digitalis was 98, and this rose to 148 after the injection of 1/25 gr. of atropin intravenously in 45 seconds. Twelve hours after digitalis (13·6 c.c.) had been administered (Case 9 in Table IV of rectal digitalis) the rate was 84, and again rose to 142 in 45 seconds, with another dose of 1/25 gr. of atropin. Unfortunately no graphic record could be obtained in this case. The second case was a woman who had been digitalis-free for 12 days. She was a hypertensive case, having a blood-pressure of 210–110. She was given 1/33 gr. of atropin intravenously, and her rate rose from 120 to 192 in 45 seconds. She was then given 15 c.c. of tincture of digitalis at the 0·125 c.c. rate, and 19 hours later, when she had slowed from 120 to 84, she was again given 1/33 gr. atropin. The rate now rose from 84 to 132 in 20 seconds (see Plate 7). This case did not show a complete release, but as the dose of digitalis proved to be too strong, causing considerable vomiting, it was felt that the dose of atropin was probably not large enough to counteract its effect completely.

It has been difficult to find enough cases to carry out this experiment more fully, but, even with the small amount of material obtained, the evidence goes far to prove that the action of digitalis by mouth, of intravenous strophanthin, and of digitalis per rectum, is alike on the vagus.

In comparing the results obtained, it has been found that digitalis by the mouth acts fully in about 6 hours, while by the rectal route the time occupied is about 8 hours. Strophanthin takes full effect, when given intravenously, in 30 minutes. The degree of slowing as represented by the change in pulse-rate is 39 beats for digitalis by the mouth, 48 beats for rectal administration, and 45 beats for strophanthin. T-wave inversion took place 8 times in 18 cases by mouth, 4 out of 5 cases by rectum, and 4 out of 15 cases after strophanthin. Vomiting occurred in 50 per cent. of the rectal cases, and with only half that frequency by the other routes. Extra-systoles showed themselves in one-third of all cases. It has been concluded that a full and similar therapeutic effect could be obtained by digitalis by mouth at the rate of 0·125 c.c. per lb. body-weight, the same preparation by rectum at the rate of 0·100 c.c. per lb., or a single intravenous injection of 1/33 gr. of strophanthin.

The average time taken for the complete elimination of a massive dose of digitalis by mouth, i.e. when it is again necessary for the patient to return to a maintenance dose, was, in the series of cases studied, about 12 to 13 days. Eggleston (11) and others give the time as 2 weeks. When given per rectum the time did not differ greatly from that of dosage by mouth, and in

the cases studied the average period of elimination was 13 days. The period of elimination after intravenous strophanthin, as one would expect, was shorter than in the two preceding methods, though not so short as some writers would lead one to expect. In the series of cases studied, the average length of time which elapsed before it was necessary to return to a maintenance dose was 8 days.

Grünbaum (6) considers the period to be 48 hours, and von Hoesslin (7) 2 to 3 days. This may account for the number of fatal cases they record as, in our experience, the patients would not have been considered sufficiently free of the drug to be prepared for further dosage.

Table V shows the duration of effect of doses of intravenous strophanthin.

TABLE V

Duration of Effect of Intravenous Strophanthin

No.	Age.	Sex.	Dose of stroph. in grs.	Oedema.	Diuresis.	Return to maintenance digitalis.
1	40	F	1/33	nil	no record	In 4 days
2	35	F	1/50	no record	no record	In 6 days
3	44	M	1/25	nil	nil	In 6 days
4	37	M	1/25	?	+	In 7–8 days
5	57	F	1/25	nil	nil	In 10 days
6	42	F	1/33	nil	nil	No record
7	69	F	1/33	nil	nil	No record
8	53	M	1/33	nil	no record	In 11 days
9	48	M	1/33	nil	no record	Put on quinidine in 3 days
10	58	M	1/33	nil	+	In 10 days
11	49	M	1/33	nil	no record	In 3–4 weeks
12	18	F	1/33	+	+7-32 oz.	Death 9 days later. No rise in speed
13	51	F	1/25	+	+18–54 oz.	In 7 days
14	54	F	1/33	nil	no record	In 15 days

Conclusions

1. A massive calculated dose of the tincture of digitalis, at the rate of 0·125 c.c. per lb. body-weight of the patient, when administered by mouth in a single draught, is the method of choice in treating cases of auricular fibrillation, because a perfectly good result can be obtained with certainty in six to eight hours.

2. In cases of vomiting from congestive failure an equally good result may be obtained by giving a similar massive dose per rectum, calculated at the rate of 0·1 c.c. per lb. body-weight.

3. In very urgent cases, where a still more rapid action is required, a similar result may be obtained within thirty minutes by the administration of a single intravenous dose of 1/33 gr. of strophanthin.

4. The site of action in all three routes is similar, i.e. that they all act via the vagus, as shown by ' vagal release ' with atropin.

5. Cases of auricular fibrillation should be given the advantage of being treated by one or other of the methods described, in order that their discomfort may be relieved in a day, instead of having it prolonged to a week by the use of older methods.

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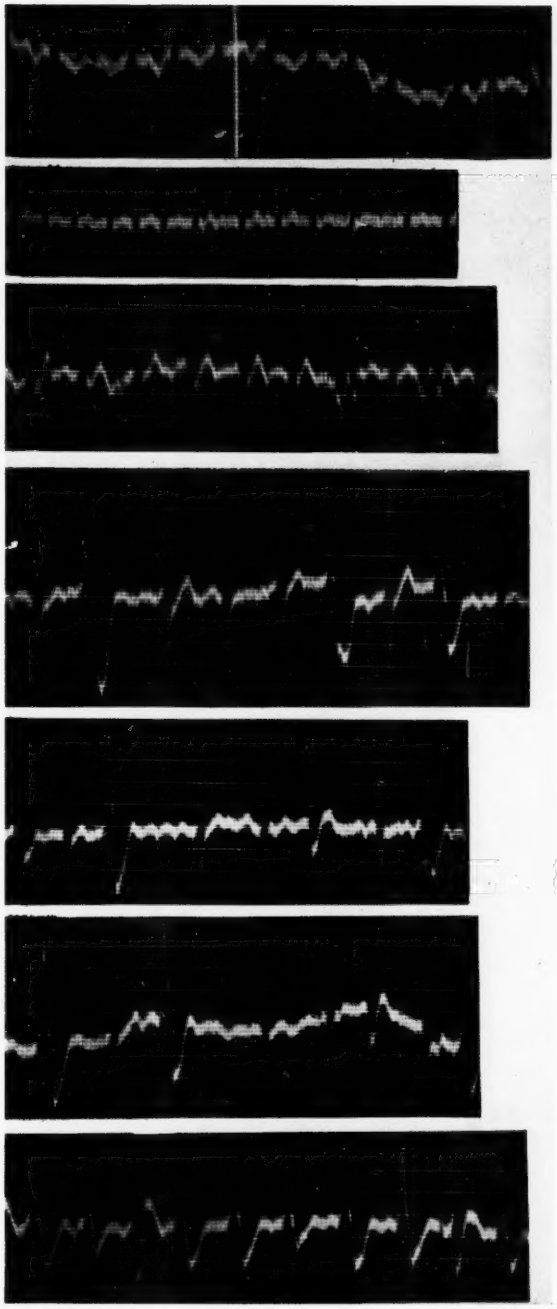
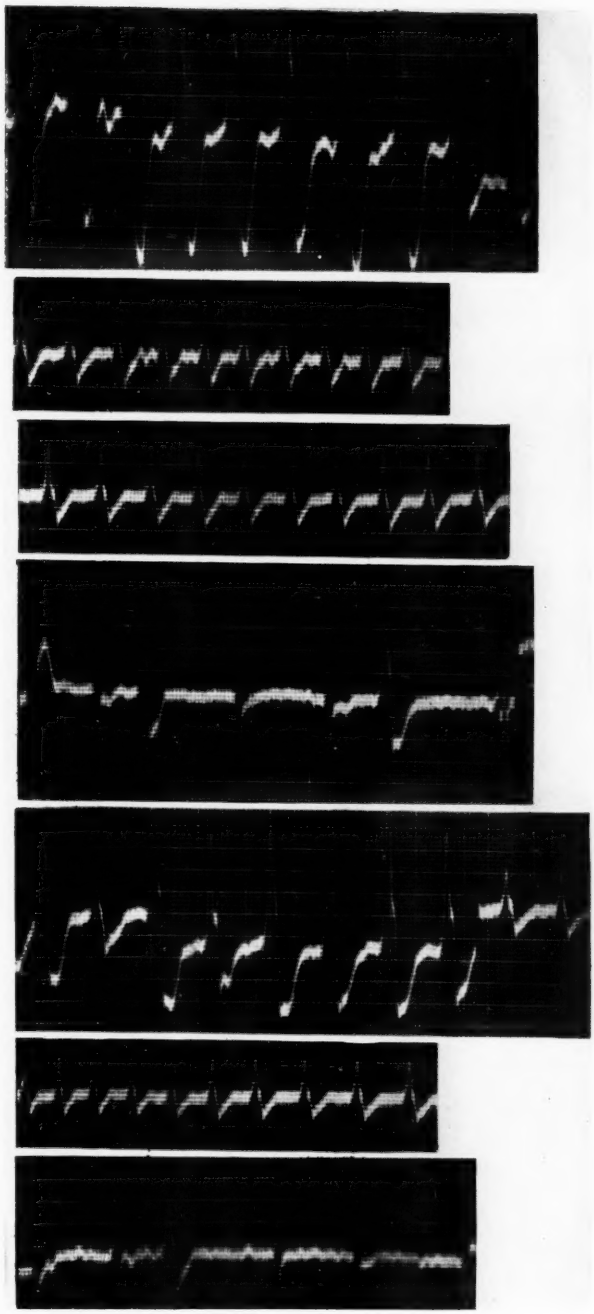


Toxic effects of $\frac{1}{25}$ grain of intravenous strophanthin.

Annie T. aged 51; cardiac symptoms 2 years; no digitalis for several months; fibrillating; liver below umbilicus. $\frac{1}{25}$ grain of strophanthin given; tracings taken at intervals subsequently; nausea after 12 minutes.

V = ventricular rate



7 min. after
V = 120

8 min. after
V = 120

12 min. after
V = 120

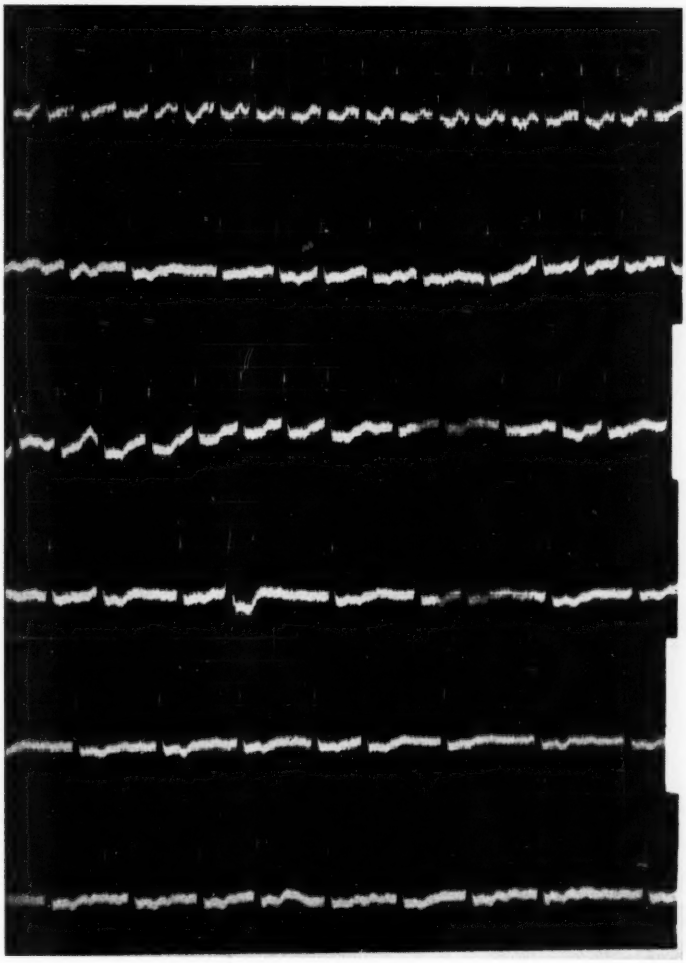
14½ min. after
V = 72

17 min. after
V = 120

18½ min. after
V = 120

23 min. after
V = 72

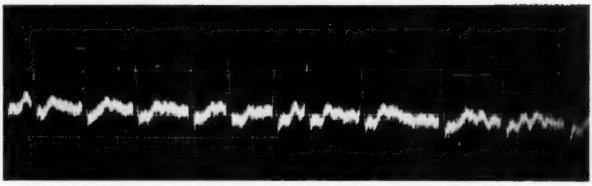
V = ventricular rate



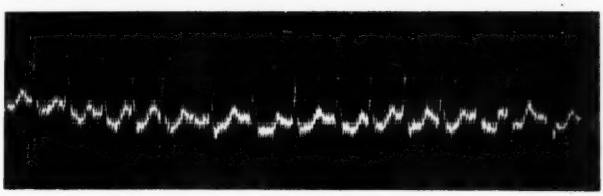
Intravenous strophanthin. E. M.—r. F. aged 64. Dose $\frac{1}{25}$ grain.

V = ventricular rate

BEFORE DIGITALIS

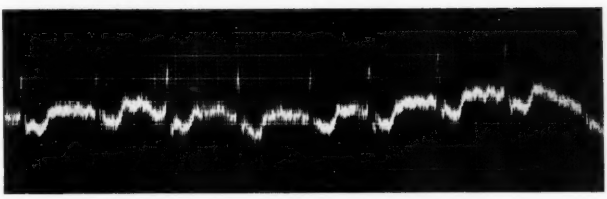


Before atropin
V = 120

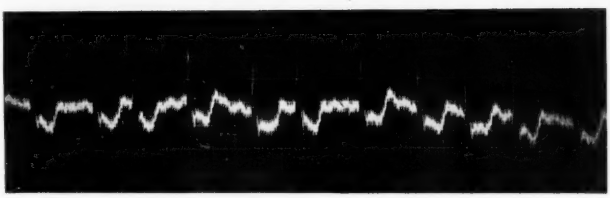


45 sec.
After atropin
gr. $\frac{1}{33}$
V = 192

19 hours after tr. digitalis 15 c.c.



Before atropin
V = 84

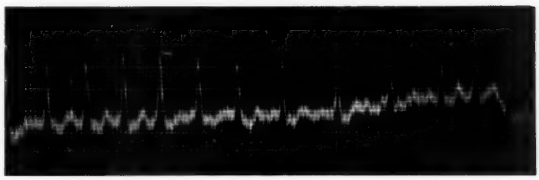


20 sec.
After atropin
gr. $\frac{1}{33}$
V = 132

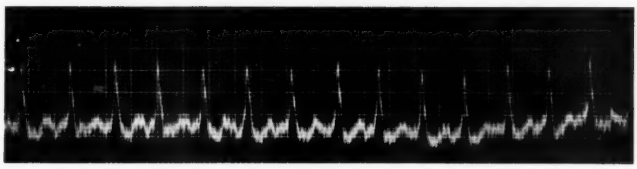
Atropin release before and after digitalis per rectum.

V = ventricular rate

BEFORE DIGITALIS

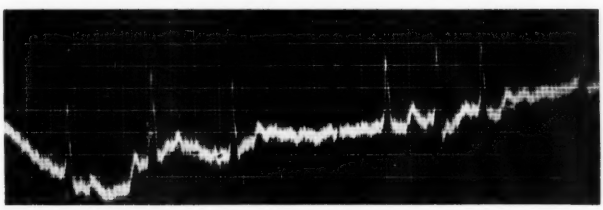


Before atropin
V = 156

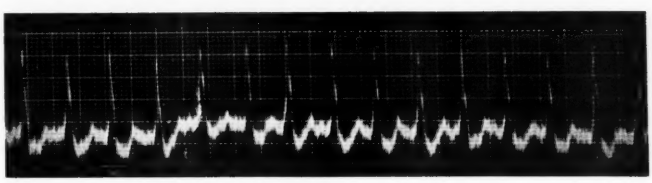


20 sec.
After atropin
V = 180

AFTER DIGITALIS
Digitalis dose 15 c.c. (0·150 c.c. per lb.)



Before atropin
V = 84



60 sec.
After atropin
V = 180

Case B, aged 41. Atropin release before and after massive digitalis dosage by mouth.

V = ventricular rate

616.36–073.75
616.41–073.75

HEPATO-LIENOGRAPHY BY THE AID OF THOROTRAST—ITS USES AND DANGERS[1]

By P. H. WHITAKER, T. B. DAVIE, and F. MURGATROYD
(From the Royal Infirmary, Liverpool)

With Plates 9 to 12

Until quite recent times radiology has contributed little towards our knowledge of the physiology and pathology of the liver and spleen. The outline of these organs can in selected cases be visualized by the use of the Potter-Bucky diaphragm and a low kilo-voltage. Various attempts at improving the results obtained by direct radiography have been made, chief of which are the use of contrast media in the stomach and colon, the creation of an artificial pneumo-peritoneum, and the intravenous injection of tetra-iodo-phenol-phthalein. None of these methods has been particularly successful, and at most they have been able to indicate the size of the organs, while failing to assist in the diagnosis of diseases affecting the liver and spleen.

In 1929 the Japanese worker Oka (1) discovered by chance that in animals injected with a thorium sol the spleen and liver became radiologically visible. In 1930 Radt (2) followed this up by elaborating the technique, and claimed to have prepared a thorium-dioxide sol which, both in his experimental and clinical work, had proved satisfactory and free from harmful effects. The preparation used by Radt is now obtainable under the trade name of 'Thorotrast' (Chemische Fabrik von Heyden).

In 1931, and during the present year, a number of papers have appeared, chiefly in American and continental publications, giving the results obtained by the use of thorotrast for purposes of hepato-lienography, retrograde pyelography, and arteriography. For purposes of hepato-lienography the preparation is administered intravenously in small doses over a fairly prolonged period, and its value and dangers have been variously evaluated by different authors. Stewart, Einhorn, and Illick (3) found that the liver and spleen were well delineated, but experienced some unpleasant immediate reactions and were sceptical as to whether the results obtained justified its use, except in unusual and selected cases. Lewisohn (4) had no ill effects in his human cases, but found evidence of histological damage to the organs in animal experiments, and concluded that its use as an aid to the clinical

[1] Received August 13, 1932.

diagnosis of disease of the liver and spleen was limited. Tripoli, Haam, and Lehman (5) considered it non-toxic and of value in research in connexion with the evaluation of liver and spleen functions. Kadrnka (6) recommends it as being, with certain exceptions, without risk, and a valuable aid to hepato-lienography.

In June 1931, by the courtesy of the firm of von Heyden, we obtained a supply of the preparation, and, following a series of animal experiments, used it in two human cases. Histological examination of the liver of the second case, obtained *post mortem* three weeks after the thorotrast injections, led us to conclude that the intravenous use of this preparation might not be as free from risk as the literature then available, and our own earlier animal experiments, had appeared to indicate; and we accordingly offered a preliminary report of our findings to Mr. C. Thurstan Holland for inclusion in his radiological section of the *Medical Annual for 1932* (7). We also carried out a further series of animal experiments with the object of investigating the pathological effect upon the reticulo-endothelial system in general, and upon the liver in particular. As a result of these observations we decided that we would limit our use of thorotrast in humans to two classes of cases only, viz. (*a*) to at least one case in which, by reason of advanced malignant disease, death in the near future was assured; this case we hoped would help us to decide whether the toxic changes observed in our second case were due to the thorotrast, or merely coincidental; and (*b*) to cases in which the possible risks of the use of thorotrast were overshadowed by its value as an aid to the exact diagnosis of hepatic or splenic lesions, and in which active treatment would result from such diagnosis. One example of each of these two types of cases have now been investigated, and the results of our findings are set out in the following pages.

Clinical Summaries of the Four Human Cases

Case 1. W. R., male, aged 59. Diagnosis: carcinoma of cardiac end of stomach. Hepato-lienography undertaken with a view to determining presence or absence of liver metastases. Dosage: 60 c.c. thorotrast. Result: liver and spleen well visualized, no secondary deposits seen (Fig. 2). Clinical effects: nil immediate or remote (6 months). Patient returned to home in country and was lost sight of.

Case 2. J. H., male, aged 65. Diagnosis: large mass in left hypochondrium, ? spleen. Hepato-lienography undertaken for purposes of diagnosis. Dosage: 75 c.c. thorotrast. Result: liver well delineated, spleen not visible (Fig. 3). Clinical effects: nil immediate. Post-mortem findings—three weeks later: the mass found to be a large, necrotic, infected retroperitoneal sarcoma. The spleen was small and shrunken, and was displaced upwards and backwards by the growth. Death due to malignant cachexia and extensive hypostatic pneumonia.

Case 3. C. W., male, aged 50. Diagnosis: carcinoma of right bronchus with hepatomegaly. Hepato-lienography undertaken to determine cause of

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enlargement of liver, i.e. ? malignant metastases. Dosage: 75 c.c. thorotrast. Result: liver outline poor, but multiple metastases visible. Spleen outline only moderate (Fig. 4). Clinical effects: nil immediate. Post-mortem examination—fortnight later—confirmed clinical and radiological findings.

Case 4. J. S., female, aged 22. Clinical history of acute abdominal crisis with abdominal pain, vomiting, cyanosis, loss of consciousness, and transient urticaria. Examination revealed enlarged liver and moderate eosinophilia—14 per cent. Diagnosis: allergic crisis due to leaking hydatid cyst in liver. Hepatography undertaken to confirm diagnosis and to localize cyst. Dosage: 50 c.c. thorotrast. Result: liver—moderate delineation, hydatid cyst localized in antero-inferior portion of right lobe. Spleen outline poor (Fig. 5). Subsequent history: operation four weeks later. Hydatid cyst marsupialized. Complete recovery after very stormy convalescence.

Technique and Dosage

In the animal experiments the rabbits used were given one or two doses of thorotrast intravenously, the dosage being based on the body-weight of the animals and being roughly proportionate to the maximum dosage recommended for human beings.

In the four human cases the administration of the thorotrast was carried out on the lines indicated by Radt (2). The preparation, warmed to body temperature, was injected slowly via the intravenous route. The first dose was 20 c.c. and the first radiogram was taken twenty-four hours later. In no case was this single dose found sufficient to show up the liver and spleen with any degree of clarity. A second dose of 20 c.c. was again followed by a radiogram after a further twenty-four hours. The liver, and sometimes the spleen, were now visible, but in all four cases it was considered necessary to give further injections of 10 or 20 c.c., and in two of the cases a fourth dose of 15 c.c. was given. The dosage employed was higher than that of the tabulated scheme of Kadrnka (6), and it is possible that the pathological effects as seen in histological examination may be, in part, due to this excess. The quantities administered by us were roughly proportionate to the relative body-weights of the patients.

The radiograms were taken with the Potter-Bucky diaphragm, the patient lying on his back. Details of exposure and penetration were the same as are used in examination of the urinary tract, e.g. in pyelography.

Clinical Effects

The immediate effects of the injection were negligible. Three of the four patients showed transient slight rises of temperature, and in one patient examined there was a slight eosinophilia not previously present. No patient suffered from the nausea, vomiting, and haemorrhage which affected some of Stewart's (3) cases. With regard to remote effects, the one case seen six months after the injection did not complain of any ill effects. Two of the patients died from causes not connected with the injection, within three weeks. The fourth patient (Case 4) showed no ill effects for four weeks, i.e.

up to the time of her operation. As indicated in the clinical summaries, she went through a very stormy convalescence following her operation, but it is impossible to determine the part, if any, played by the thorotrast in determining this condition.

Radiological Findings

In the animal experiments the spleen was found to show up with greater clarity than the liver. Some degree of structural detail is apparently visible in the case of the spleen, as the radiographic shadow is seen to be finely mottled by minute rounded areas of translucency. These mottlings, we believe, represent the small areas around the malpighian corpuscles in the cortex, which are relatively free from phagocytic reticulo-endothelial cells as compared with the pulp and reticulum of the deeper parts of the spleen. The liver shadow is homogeneous except for the variations of shadow density determined by the variations of thickness of the organ. We were unable to satisfy ourselves that the deposition of thorotrast in the bone-marrow, lymph-glands, or lungs produced any definite increase of radiographic density in the radiograms we obtained (Fig. 1).

In our human cases the liver has usually shown up with greater clarity than the spleen. In none has there been radiographical evidence of the normal internal structure of these organs. The shadows are homogeneous even in the case of thin slices of the injected organs. In these the thorotrast-injected liver shows up with increased density, but there is no evidence of the parenchymatous or biliary structural arrangements, while the vascular tree is depicted with no greater clarity than in uninjected livers.

With reference to pathological lesions Radt (2) claimed that gross structural changes of the liver were demonstrable in those cases where parenchymatous and storage cells were destroyed either by connective-tissue proliferation, e.g. in cirrhosis, or by malignant metastases. We have not used thorotrast in any case of cirrhosis of the liver, but our results have confirmed his claim in connexion with secondary malignant deposits (Fig. 4). It is noteworthy, however, that in this case the metastases were extremely numerous, and we are not convinced that the method employed would be capable of demonstrating the presence of small scanty metastases. Lewisohn (4) was unable to demonstrate metastases in his cases, and in this connexion, too, it may be noted that Stewart and his collaborators (3) were unable to demonstrate anything more than hepato-megaly in their case of cirrhosis of the liver. Radt premised further that thorotrast would render radiographically visible such lesions as abscesses, hydatid cysts, haemangiomas, etc., and in Case 4 (Fig. 5) the correctness of this has been confirmed in the case of hydatid cyst of the liver. Here the liver shadow, in the print, is slightly reduced in density over the cyst area, but the identity of the cyst is determined essentially by the dark outline of the capsule, where the reticulo-endothelial cells are presumably concentrated by compression from the cyst.

The elimination of the thorotrast will be discussed in the section dealing with the pathological effects, but here it may be noted that, both in the animal experiments and in the human case examined six months after injection, the radiological findings appear to indicate that elimination of the thorotrast, if it occurs at all, is extremely slow. No decrease in density could be discerned in the shadows of the liver and spleen in radiograms taken after the lapse of six months. Stewart (3) noted a similar persistence of the shadow in one case after eight months.

Pathological Findings

Animal experiments. In the animals inoculated in June, 1931, before we used thorotrast in any human cases, the effects considered were mainly clinical. The immediate and relatively remote effects appeared to be consistent with the claim made by the makers of the preparation that it was innocuous. At this time sections of liver, kidney, etc., were examined in the case of one of the animals killed for the purpose, but the changes found were considered to be negligible. Following the discovery of a peculiar focal necrosis of the liver in the second human case, during the routine examination of the organs obtained *post mortem*, a further series of rabbits was injected, and the organs were examined at varying intervals after the injection. Attention was directed particularly to changes produced in the liver, but the other organs which might reasonably be expected to show changes were also examined. It may be stated at once that although pathological changes (*vide* below) were observed in the liver, and, to a lesser extent, in other organs of these animals, in no case was there found such a degree of toxic degeneration as was present in at least two of the human cases. This we believe to be due to the fact that in the animals there were no additional complicating and aggravating toxaemias from other conditions of disease such as were present in the human cases. It is of the utmost importance that this difference between the animal and the human findings should be stressed when assessing the value and dangers of this aid to hepato-lienography.

The effect of the thorotrast injection as judged by the histological pictures of the organs examined appears to be that of a moderate degree of toxaemia. The effect is noticeable within twenty-four hours after the injection, and appears to become progressively slightly worse for the next few days, sections from animals killed on the fourth day appearing to present the maximum changes. By the tenth day the changes are slightly less marked, and by the end of two months a further improvement in the toxic effect is noticeable, but other new changes have appeared. The changes appearing in the different organs are as follows:

Liver. In the early stages the thorotrast can be readily seen collected in the Kupffer cells. In these the injected material is aggregated in small, brightly refractile, slightly yellowish granules (in haematoxylin and eosin-stained sections). The Kupffer cells are only slightly enlarged, and their

small, darkly-staining nuclei can in most cases be seen at the peripheries of the cells. On the fourth day (Fig. 6) the hepatic cells show a maximum degree of the cloudy swelling apparent to a slightly lesser degree in the sections on the first day. The cells show marked swelling and a coarse granularity of the cytoplasm. The nuclear changes are slight. In the later specimens the cloudy swelling is slightly less pronounced, but the thorotrast-filled Kupffer cells become more prominent. They are about twice normal size, and most of them show multiplication of nuclei, three or four of the typical nuclei being usually visible at the periphery of the granular masses. The refractile granules, too, are more distinct and discrete. These changes appear to indicate (1) a further accumulation of thorotrast in the liver, possibly by the gradual elimination of the material originally retained in other parts of the body, and (2) either an unsuccessful attempt on the part of the Kupffer cells to divide, or an aggregation of Kupffer cells in small clusters as the result of active migration.

Spleen. Large amounts of thorotrast are readily seen filling the reticulo-endothelial cells. Changes of a toxic nature are not discernible, and the only further comment to be made is that, in the later specimens, there is no apparent diminution of the amount of thorotrast, but a tendency of the granule-filled cells to aggregate in clusters of four to ten or more (Fig. 7).

Marrow. The nature of the changes here are similar to those described in the spleen. It is to be noted that the megakaryocytes show no evidence of phagocytic propensities towards the thorotrast.

Lung. In the earlier specimens the thorotrast is visible in large clear cells in the walls of the alveoli. These cells project into the lumen, and in a few cases are seen free in the alveoli. In the later specimens these phagocytic cells are not distributed so widely, but appear in small groups, usually at the angle of junction of alveolar walls, and no longer appear to project into the alveoli. No pathological effect is noticeable in the lung tissue.

Kidney. In the early specimens very little thorotrast is visible in this organ, only an occasional granule being visible in the glomeruli; but nowhere are there any cells filled with the typical granules. The parenchyma of the kidney shows very little toxic change, by which it would appear that the deleterious effects of injection are probably limited to parenchymatous cells in close proximity to collections of the material. In later specimens there is a slight increase of the granular material in small collections in the glomeruli, where it appears to be present in the capillary walls.

Suprarenal. Medium-sized cells in the cortex are seen filled with thorotrast. These cells are never very numerous, and are found chiefly between the columns of cells in the zona fasciculata, to a lesser extent in the zonae glomerulosa and reticularis, and not at all in the medulla. No marked change is noticeable in the later specimens, nor is there noticeable any definite pathological effect on suprarenal parenchyma.

It will be noted that in these animals the thorotrast is collected almost entirely in the cells of the reticulo-endothelial system, where it remains in apparently undiminished concentration for long periods, thus producing at least a partial blockade of this system. In the liver, where toxic effects are most easily studied, the effect is a definite and quite pronounced degree of cloudy swelling of the hepatic cells, which, though diminished slightly in degree with time, is present even at a late date after the injection.

Human cases. In connexion with the pathology of the human cases we have restricted our attention to a study of the liver changes.

Case 1. No operative measures were undertaken, and the patient was lost sight of after his return for a second X-ray examination six months after his injection. No pathological examination was thus possible.

Case 2. At the post-mortem examination on this man, performed three weeks after the thorotrast injection, the mass believed originally to have been an enlarged spleen was found to be a foul-smelling, infected, necrotic, retroperitoneal sarcoma. Early generalized peritonitis was present and, in addition to these two sources of toxaemia, there was a severe hypostatic pneumonia affecting both lungs. The spleen was small and shrunken, and displaced upwards and somewhat backwards by the growth. It is possible that interference with the blood-supply by the pressure of the growth on the splenic vessels may have accounted, in part, for the poor delineation of the splenic shadow in the radiogram taken, though it is more probable that this shadow was obscured by that of the tumour mass itself. The liver contained no malignant metastases, but showed some obvious fatty change and toxic cloudy swelling.

Histological examination of the liver showed an unusual picture (Fig. 8). In addition to the masses of thorotrast concentrated in the Kupffer cells there was, throughout the liver, evidence of a wide-spread necrosis affecting the hepatic cells. Many of the remaining liver cells showed apparent hypertrophy, others showed decentralization of their nuclei, and some nuclei showed hyperchromism. It was this marked and unusual necrosis which prompted us to prepare the preliminary note of our findings, which was incorporated in the radiology section of the *Medical Annual* (1932).

Case 3. In this case a rapidly fatal termination as a result of carcinoma of the bronchus appeared to be assured; and, as the case offered an opportunity for testing both the efficacy of thorotrast for demonstrating the presence of suspected malignant metastases in the liver, and the confirmation or refutation of the presumed toxic effect upon the hepatic cells found in Case 2, a course of intravenous thorotrast injections was given. Histological examination of the liver obtained *post mortem* about fourteen days later (Fig. 9) showed a definite but milder degree of necrosis compared with that seen in Case 2. The hepatic cells not affected by necrosis are swollen and granular, and in most there is obvious migration of the nucleus to the periphery of the cell. The nuclei are small, and many show hyperchromism; and there is a suspicion of hyperplasia of the liver tissue in some areas. The appearances suggest toxic degeneration with early incomplete recovery.

Case 4. The presence of a presumably leaking hydatid cyst in this otherwise healthy young woman had caused a very severe allergic crisis, from the effects of which she had apparently completely recovered at the time of the operation about six weeks later. At the operation a small fragment of liver was excised from the superior surface of the liver as far removed as possible from the situation of the hydatid cyst, and this fragment was immediately fixed in formalin. Sections of this liver (Fig. 10) show the usual typical thorotrast-filled Kupffer cells and also minute collections of granules apparently between the cells. A very marked degree of cloudy swelling of the hepatic cells, amounting in places to definite necrosis, is the chief

feature of the section. Many nuclei show hyperchromism, and some also show a tendency to peripheral migration. Here it seems most unlikely that any factor other than the effect of the thorotrast can be incriminated as the cause of these toxic changes in the liver. We therefore feel justified in assuming that the minimum effect of thorotrast on the liver is the production of severe cloudy swelling, which may proceed to necrosis in those cases where any other toxic influence is already acting on the hepatic cells. The subsequent history of this patient is interesting. Following the operative removal of the endocyst of the hydatid and the marsupialization of the cavity, the patient appeared to progress satisfactorily for a few days but then developed a pyrexia with abdominal signs indicative of a peritonitis. She was drained supra-pubically, a small quantity of thin purulent fluid being evacuated; and, after a very severe illness, made a slow but complete recovery. To what extent the partial blockade of her reticulo-endothelial system contributed to this relapse, by interference with the mechanism for antibody formation, is an interesting but unproductive line of speculation.

Discussion

The claim put forward by the makers of thorotrast, that this preparation is an efficient aid to the radiographic visualization of the liver and spleen, and of some of the lesions affecting these organs, is well substantiated by the experience of others as well as of ourselves, but that it is innocuous to animals and humans is by no means certain. Among the immediate clinical effects which have been observed are vomiting and haemorrhages (3), slight fever with or without chills, diarrhoea, and headaches (1). In our four cases slight transient pyrexia has been the only immediate clinical effect noted. In the majority of all recorded cases, however, the effects are regarded as of a negligible character, and no fatal result has been recorded. Evidences of tissue damage have also been observed in some cases, of which the chief are acute splenitis (3), nuclear damage and evidence of tissue repair (4), parenchymatous and glomerular damage in the kidneys with large doses (8), while our own observations indicate a toxic effect upon the liver cells.

These results are, we feel, of sufficient importance to call for caution in the use of this preparation. In these days when the intravenous administration of drugs and preparations intended as diagnostic aids is carried out with a frequency which savours of the contempt bred of familiarity, the capacity for deleterious effects of some of these preparations is apt to be overshadowed by their immediate value. This is excusable only when the cell damage is slight and early recovery is possible. In the light of such criteria the advantages and disadvantages of the use of thorotrast as an aid to the diagnosis of lesions of the liver and spleen may thus be set off against each other.

The advantages are: (*a*) Clear radiographical visualization of liver and spleen is made possible for purposes of differential diagnosis of palpable or

otherwise discernible abdominal masses, tumours, &c.; (*b*) Enlargement of these organs not otherwise determinable is made evident; (*c*) Malignant metastases, at least when numerous or large, can be demonstrated in most cases; (*d*) Other lesions, e.g. abscesses, hydatids, tumours, cirrhosis, &c., are diagnosable in some cases.

The disadvantages are: (*a*) Immediate objectionable clinical effects follow in a few cases; (*b*) Some cytological damage is probable in the liver and spleen—the effect, which is apparently a toxic one, may in some cases be severe; (*c*) The reticulo-endothelial system is, at least partially, blockaded for some time, if not permanently; (*d*) On account of the extremely slow elimination of the thorotrast the tissues containing large numbers of cells of the reticulo-endothelial system are subjected, over long periods, to a radio-active influence.

With regard to the advantages, little further need be said except to draw attention to the fact that the exact diagnosis of some of the lesions included under general terms in the above list is almost impossible without the aid of some such method of visualization as that afforded by thorotrast injection. For these carefully selected cases thorotrast, or some similar preparation, will in future be regarded as invaluable, if not essential.

The disadvantages specified under (*a*) and (*b*) have been dealt with. The partial blockade of the reticulo-endothelial system acquires its chief importance on account of its long duration. If the cells of this system are, as is believed, concerned with the elaboration and mobilization of the antibodies specific to many bacteria and toxins, it is almost certain that this function is dependent upon the ingestion of foreign particulate matter by these phagocytic cells. A blockade, even partial, of these cells assumes then a serious aspect, and particularly if this blockade persists for any length of time. The appearance of the thorotrast-filled cells both in the animal and human livers and spleens examined at various intervals after injection appears to indicate a marked reduction of their further phagocytic capacity. The stormy convalescence of the one patient (Case 4) in whom we have had the opportunity of observing the reaction to an intercurrent infection, shortly after the thorotrast injection, may well have been, in part, the effect of this interference with the function of the reticulo-endothelial system. This aspect of the effect of thorotrast injections is, however, not one which readily lends itself to accurate scientific evaluation, though animal experiments carried out on a very large scale with controls may some day settle this problem.

The possibly detrimental effect resulting from the intrinsic radioactivity of the thorium dioxide remains to be considered and cannot lightly be dismissed as negligible. The spleen of one of Stewart's (3) injected cases, left in contact with a photographic plate for twenty-four hours, produced an image of itself, while control spleens had no such effect. This would not be of much significance were it not that here again the time factor is favourable to the production of ill effects; and it is at least possible that

some of the effect on the liver cells described here may be the result of this slight, but maintained, radioactivity.

In conclusion, we feel justified in calling for caution in the use of this aid to the radiographic visualization of the liver and spleen (and arteries); and in suggesting that, until further and fuller experiments and investigations have determined the degree of toxicity, &c., possessed by this preparation, its use should be restricted to those cases in which the adoption of an active and fruitful line of treatment depends entirely upon the exact diagnosis and localization of lesions made possible by this aid to hepatolienography.

Acknowledgements. We wish to take this opportunity of expressing our indebtedness to Dr. John Hay and Mr. R. E. Kelly of the Liverpool Royal Infirmary and to Dr. H. H. MacWilliam and Mr. W. S. Brindle of Walton Hospital for permission to investigate the cases described, for access to their case records, and for their willing co-operation in this work. We are also indebted to Dr. R. E. Roberts of the radiological department of the Royal Infirmary for his assistance in connexion with the radiographical section of the paper.

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FIG. 1. Rabbit, 48 hours after full injection. Spleen more sharply delineated than liver.

FIG. 2. Human Case No. 1. Liver and spleen both well delineated, no lesions visible.

FIG. 4. Human Case No. 3. Spleen outline well shown in upper left-hand corner. Liver filling whole abdomen, outline not visible, but showing numerous translucent areas representing malignant metastases.

FIG. 3. Human Case No. 2. Liver well shown, spleen outline very faint, displaced upwards by sarcomatous mass shown centring over midpoint of 11th rib.

FIG. 5. Human Case No. 4. Spleen faintly outlined. Hydatid cyst in lower portion of right lobe of liver; upper border at level of 11th dorsal vertebra, lower border at level of 3rd lumbar interspace.

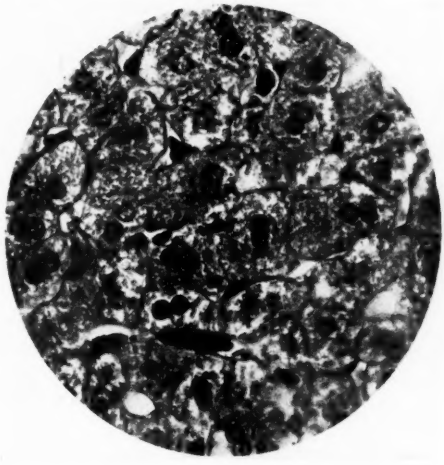

FIG. 6. Rabbit's liver 4 days after injection. Thorotrast in Kupffer cells (show dark). Advanced stage of cloudy swelling and divided nuclei in hepatic cells. × 450.

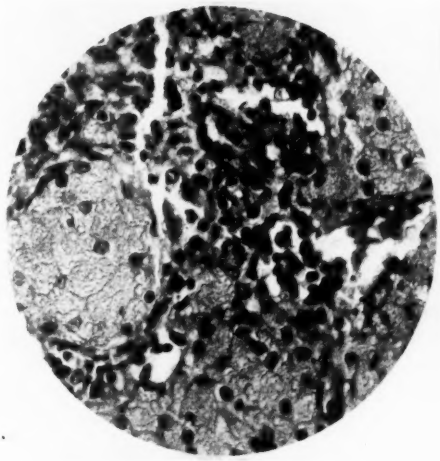

FIG. 7. Rabbit's spleen. 2 months after injection, showing aggregations of cells filled with thorotrast: large pale granular cells. × 350.

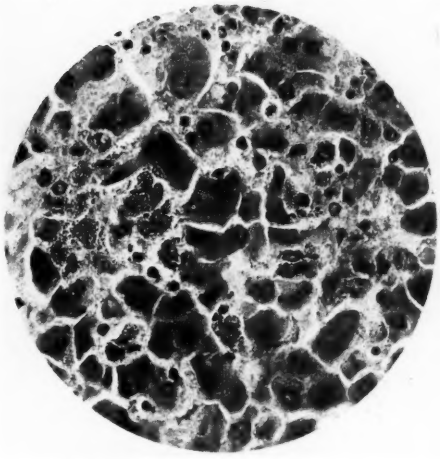

FIG. 8. Liver. Human Case No. 2. Diffuse necrosis, especially around Kupffer cells filled with thorotrast granules. × 350.

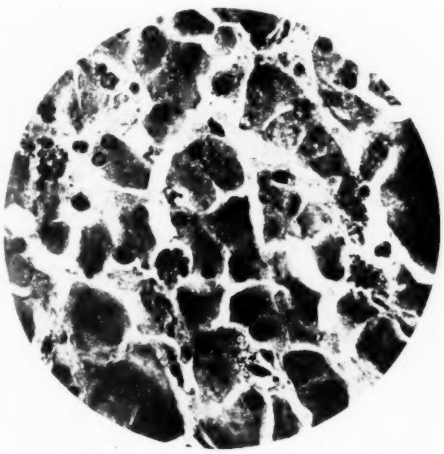

FIG. 9. Liver. Human Case No. 3. Slight necrosis. Peripheral migration of nuclei. × 400.

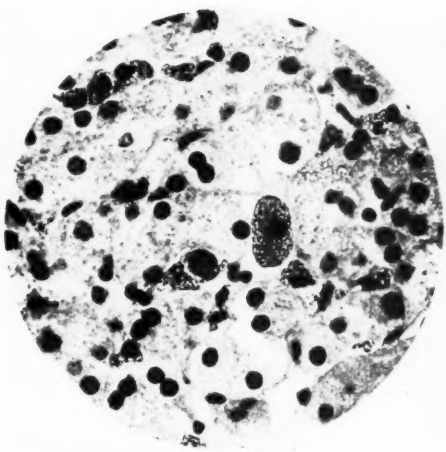

FIG. 10. Liver. Human Case No. 4. Extreme cloudy swelling. Hyperchromism of nuclei. Thorotrast granules in Kupffer cells and also in scattered granules between hepatic cells. × 400.

616.33–006.463

LINITIS PLASTICA: A STUDY OF TEN CASES[1]

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With Plates 13 and 14

Definition. Linitis plastica is a term designating clinically a skiagraphic and, in the post-mortem room, a gross contraction of the stomach, caused most frequently by a fibrosing cancer, occasionally by syphilis, and, possibly, in rare cases, by a simple inflammatory process. The fibrosis involves chiefly the submucosa and to a less extent the other layers, sometimes extending to the connective tissue in the region bordering on the stomach.

Synonyms. There are no fewer than forty-two names for this condition. Arranged in chronological order they are: hypertrophy of the mucous membrane (Andral 1829 (1)); hypertrophy with induration and hypertrophic stenosis of the pylorus (Cruveilhier 1835 (24)); hypertrophy of the stomach (Hare 1853 (57)); fibroid induration (Jones 1855 (73)); sclerosis ventriculi (Snellen 1856–7 (124)); cirrhosis of stomach (Brinton 1857); linitis plastica (Brinton 1865 (15)); fibroid disease (Wilks 1862 (144)); fibroid infiltration (Boulton 1862 (9)); fibroid degeneration (Habershon 1866 (53)); hypertrophy of the walls (Fox 1868 (46)); hypertrophische Stenose des Pylorus (Nauwerck 1878 (102)); cirrhotische Verkleinerung des Magens (Nothnagel 1879 (103)); gastrite scléreuse (Durand-Fardel 1879 (35)); absolute primitive atrophy (Fenwick 1880 (42)); sclérose sous-muqueuse hypertrophique (Hanot et Gombault 1882 (55)); Magenschrumpfung (Schnetter 1884 (120)); fibrous contraction (Turner 1887 (133)); sclerosirende Gastritis (von Kahlden 1887 (139)); hypertrophic cirrhosis (Formad 1887 (45)); cirrosi gastrica (Viti 1887 (134)); phthisis ventriculi (Meyer 1889 (101)); cancer conjonctif sous-muqueux et rapproché des sarcomes fusocellulaires (Garret 1892 (48)); diffuse infiltrating carcinoma (Welch 1893 (143)); stenosirende pylorushypertrophie (Tilger 1893 (129)); Endotheliome (Hansemann 1896 (56)); stenosirende Gastritis (Boas 1898 (6)); épithéliome diffus (Duplant 1899 (34)); endogastritis obliterans (van Leersum-Rotgans 1899, quoted by von Cackovic) (137); hypertrophic gastritis (Hemmeter and Stokes 1900 (63)); Zuckergussmagen (von Sury 1907 (142)); primäres Magensarkom (Hosch 1907 (66)); péritonite nodulaire sclérogène sténosante (Curtis 1908 (26)); leather-bottle stomach (Stretton 1909 (127)); pachygastrite cancéreuse (Delamare and Brelet 1909 (31)); gastrointestinale

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Sklerostenose (Krompecher 1910 (79)); fibromatosis of stomach (Thomson and Graham 1913 (128)); chronic interstitial gastritis (Sailer 1914 (116)); gastritis phlegmonosa circumscripta (von Stapelmohr 1918 (141)); syphilitische Schrumpfmagen (Hirschberg 1926 (64)); sclerosing pyloric and diffuse fibrocarcinoma (Ewing 1928 (39)); carcinoma plastica (Friedenwald and Morrison 1931 (47)).

History. A careful search of the literature will reveal descriptions of scirrhous disease of the stomach as early as the latter part of the eighteenth century. These were incomplete, of course, and not entirely convincing. von Sury (142) in his excellent paper mentions the case of sclerosis of the stomach reported by Luther in 1799. However, the French clinicians, Andral (1) in 1829 and Cruveilhier (24) in 1835, left us fairly accurate accounts of the disease. The latter originally described the condition as benign hypertrophic pyloric stenosis. Bricheteau (13) in the same year reported cases of a scirrhous affection of the oesophagus and pylorus which he considered distinct from cancer. Brinton (15) in 1859 made the first attempt to establish it as a separate and distinct disease of the stomach. He gave the name of linitis plastica (Greek, *λινον*—linen cloth or net; Latin, *ex lino factum*), because, as he suggested, 'the inflammation of the filamentous network of areolar tissue, which seems to be the main characteristic of the lesion, might well be expressed by such a word as linitis'. He was by no means certain that the process was not cancerous. von Rokitansky (140) in 1854 maintained that the submucous hypertrophies of the stomach belong in reality to the group of fibroid cancers. Other English clinicians of Brinton's day, Hare (57), Jones (73), Wilks (144), Habershon (53), and Fox (46) reported cases and stressed the benign nature of the disease, which opinion received the support of Hanot and Gombault (55) as well as of Tourlet (131) of France. It was, however, considered to be a malignant process by Garret (48), Bret and Paviot (12), Hoche (65), Schacher (117), and the majority of the more recent French and Italian students. In spite of the claims of these writers, the surgeons, von Eiselberg (138), Roux (115), Sheldon (121), Jonnesco and Grossman (74), and Deaver (29) held to the benign nature of linitis plastica. von Sury (142), Leith (82), and Lyle (88) admit the supposed cancerous nature of some cases; in the words of Leith 'there is nothing inconsistent or improbable in the supposition of a simple gastric cirrhosis'; and again, 'a cirrhotic condition of the stomach may arise from a simple or a cancerous condition'. It was not until about the beginning of the twentieth century that the term 'leather-bottle' appeared with any degree of frequency in the English and American literature. As Lewald (84) says, the term 'appears to be based upon the consistency and thickness of the stomach wall rather than upon any definite resemblance to our modern bottles; though the narrowing of the pyloric end of the stomach and a compensatory widening of the cardiac end would seem to be the reason for calling it a "leather-bottle" stomach, after the leathern water-bottles of the early Egyptians'. With the advent

of improved diagnostic methods, more particularly the Wassermann test, and the barium meal with fluoroscopic and serial plate examinations, one begins to hear more frequently of the syphilitic Schrumpfmagen, syphilitic leather-bottle stomach, and the syphilitic linitis plastica. Consequently in the past few years one always considers the possibility of a given case of a small deformed stomach being of a simple inflammatory, a syphilitic, or of a malignant neoplastic origin.

Author's cases. Our own experience comprises ten cases, eight of which were typical clinically, roentgenologically, and histologically. Two others were acceptable on clinical and roentgenologic grounds, but were not proven histologically. A brief abstract of these ten cases follows.

Abstract of Proven Cases

Case 1. Female, aged 42. Diffuse round-celled sclerosing fibrocarcinoma of stomach with extension to the gastro-hepatic and gastro-colic omentum and parietal peritoneum. Palpable epigastric tumour; characteristic X-rays; symptoms of ten months' duration with distress and fullness after eating, constipation, and anaemia; laparotomy confirmed diagnosis; biopsy.

Case 2. Female, aged 54. Diffuse sclerosing fibrocarcinoma of stomach with involvement of great omentum, gastro-hepatic omentum, mesentery of small intestine and general peritoneal cavity with ascites; pyloric ulcer. Symptoms of five months' duration with picture of polyserositis, hepatic cirrhosis, and finally of intestinal obstruction. Stomach was always dilated. Pyloric ulcer with haemorrhage. Death. *Post mortem.* Histology characteristic.

Case 3. Male, aged 70. Linitis plastica involving practically all of the stomach and by extension the gastro-hepatic omentum and head of the pancreas. Death; autopsy. Histological diagnosis of small round-celled sclerosing fibrocarcinoma of stomach. Symptoms of obstruction at cardiac end of stomach. Typical water-bottle stomach. Haemorrhage.

Case 5. Female, aged 66. Linitis plastica or diffuse sclerosing fibrocarcinoma of stomach with metastases to gastro-colic omentum and glands, as well as to glands of the lesser curvature and to pancreas. Laparotomy revealed also cholelithiasis. Histological examination of tissue from omentum revealed small round-celled fibroscirrhous carcinoma. Clinical course was that of cancer of stomach.

Case 7. Male, aged 35. Linitis plastica; metastases to mediastinal, mesenteric, and retroperitoneal glands, as well as to pancreas, adrenals, and lungs. Clinical course of obstructive jaundice, polyserositis, general anasarca, and palpable mass in epigastrium. Clinical diagnosis was carcinoma of head of pancreas. Autopsy revealed a linitis plastica involving the lower end of the oesophagus and the stomach as far as the pylorus, with extension of the tumour into the pancreas, adrenals, mesentery, omentum, and along the bile-ducts and portal veins; metastases to the retroperitoneal, post-gastric, mesenteric, and mediastinal glands, as well as to mesentery of

the sigmoid and to the glands around each iliac vein. There was also an extension of the tumour into the transverse colon with numerous small nodules protruding into its lumen. Left ureter was buried in a dense mass of tumour resulting in a moderate hydronephrotic left kidney. Bladder fundus was also infiltrated by tumour. Histological diagnosis of diffuse scirrhous fibrocarcinoma of the stomach with extension or metastases to oesophagus, mesentery, peritoneum, lymph glands, pancreas, adrenals, kidney, bladder, and lungs.

Case 8. Female, aged 47. Linitis plastica of extensive grade proven by exploratory laparotomy. Biopsy diagnosis was round-celled sclerosing fibrocarcinoma: clinical history and roentgenological findings typical of linitis plastica involving the stomach and lower end of the oesophagus; moderate ascites; involvement of gastro-hepatic omentum and great omentum; uneventful post-operative recovery.

Case 9. Female, aged 37. Linitis plastica with extension into oesophagus, duodenum, and gastro-hepatic omentum. Symptoms suggested disease of upper right quadrant of abdomen and later pyloric obstruction. Signs of bilateral hydrothorax, hydropericardium, and hydroperitoneum simulating tuberculous polyserositis. X-ray diagnosis of linitis plastica. Fever, sweats, and petechiae made their appearance, followed by melaena and haematemesis. Autopsy revealed diffuse scirrhous carcinoma of stomach with dilatation and ulceration near the pylorus and spread of carcinoma into oesophagus and duodenum, as well as into the lymphatics and lymph nodes of gastro-hepatic and great omentum. There was also widespread chronic peritonitis and chronic inflammation of mesentery and wall of small bowel at its mesenteric attachment, due to tumour formation. The ovaries were enlarged and nodular. Histological diagnosis was scirrhous fibrocarcinoma of stomach, oesophagus, small intestine and its mesentery, gastro-hepatic omentum, adjoining lymph nodes, and the visceral peritoneum. Apart from the gastro-intestinal tract, the only organ of interest was the ovary, which showed typical lesions of tuberculosis.

Case 10. Female, aged 90. Linitis plastica with typical clinical and X-ray picture of water-bottle stomach. Clinical course of obstruction of cardiac end of stomach, with regurgitation of food, progressive cachexia and anaemia, terminated by broncho-pneumonia. Autopsy revealed a typical leather-bottle stomach with metastases to omentum and regional gastric nodes. The histological diagnosis was sclerosing fibro-adenocarcinoma. (See Plates 13 and 14, Figs. 1 to 6.)

Doubtful cases. Case 4. Male, aged 54. Linitis plastica (?). Diffuse sclerosing fibrocarcinoma of stomach involving the entire body of the stomach. X-ray and clinical diagnosis of linitis plastica. Clinical picture of gastric cancer. Improvement under medical management, but development of a palpable tumour in left upper quadrant. Condition inoperable and patient discharged. *No histological proof.*

Case 6. Female, aged 44. Linitis plastica; diffuse sclerosing fibrocarcinoma of stomach. Clinical course of gastric cancer with involvement of cardia. X-ray diagnosis of linitis plastica or syphilis of stomach. Two negative blood Wassermann reports. Operation refused. *No histological proof.*

Aetiology

1. *Age.* It is a disease of adult life. Lyle (88) found that in sixty-one true or *benign* linitis plastica cases, in which the age was given, the following was the incidence:

20 to 30 years	6 cases
30 ,, 40 ,, ...	13 ,,
40 ,, 50 ,, ...	17 ,,
50 ,, 60 ,, ...	11 ,,
60 ,, 70 ,, ...	12 ,,
70 ,, 80 ,, ...	2 ,,

In fifty-two *malignant* linitis plastica cases the age incidence was:

20 to 30 years	6 cases
30 ,, 40 ,, ...	9 ,,
40 ,, 50 ,, ...	10 ,,
50 ,, 60 ,, ...	12 ,,
60 ,, 70 ,, ...	11 ,,
70 ,, 80 ,, ...	4 ,,

Lyons (90) found in 33 cases proven by operation and biopsy an average age of 52 with the extremes of 70 to 34 years. Leith (82) reported the average age of occurrence in man to be about 50 and in woman somewhat under 40 years. In our series of ten cases there were two in the fourth, four in the fifth, three in the sixth, two in the seventh, and one in the ninth decade. The mean age for the series was 53·9 years.

2. *Sex.* It is more common in men than in women: thus of the benign cases in which the sex was given, Lyle found that 41 were men and 22 women; while in the malignant cases there were 33 and 19 respectively. In Lyons's series of 33 there were 23 males to 10 females, or about the usual ratio found in other forms of gastric cancer. In our series seven of the ten cases were females (70 per cent.), whereas in the gastric cancer series of 255 patients recently studied by us[2] only seventy-seven cases, or 30 per cent., were females. Leith states that the cases are almost equally divided between the two sexes.

3. *Pre-existing diseases.* There is a history of cardiac or arterial disease in a considerable number of the case reports in the literature. However, this does not seem to be any more than the expected disease incidence in patients of the cancer age. Only three of our series showed arteriosclerosis of any degree, one case both cerebral and aortic, and two others with involvement of the aorta alone. None of the acute infectious diseases loomed large in the past medical histories of these patients. Careful inquiry in our series revealed a history of influenza, erysipelas, typhus fever, chorea, or broncho-pneumonia once in each of five cases.

[2] Howard, C. P., and Fullerton, C. W., *Canad. Med. Assoc. Journ.*, 1932.

4. *Previous gastric disease.* Several authorities hint that many of the patients will reveal a story of long-standing dyspepsia, and others that even peptic ulcer may form a focus for the process. Phlegmonous gastritis was considered by von Stapelmohr (141) as an important factor in some cases. In our series one patient (Case 10) had dyspepsia for many years. Another gave a history of an acute gastro-intestinal upset a few years previously, and a third stated that he had had two attacks of catarrhal jaundice. No patient gave a clean-cut history of a peptic ulcer. Occupation trauma, as noted by Hare (57), Snellen (124), and Schacher (117), cannot be stressed in our series.

5. *Heredity.* Little or no mention is made of heredity as a role in this type of cancer, though in our small series the family history of eight was examined rather carefully. In five of these there was no known case of cancer. In one patient there was a history of cancer of the uterus in the mother. In another a maternal aunt had died of cancer of the stomach, and in a third (Case 8) both father and mother were reported to have died from cancer of the stomach.

6. *Alcohol.* Brinton's (15) suggestion that alcohol was a possible exciting cause has not received support from the subsequent study of the disease. It is true that, in our small series, abuse of alcohol was admitted by two of the male patients. However, Hanot and Gombault (55), von Sury (142), and Krompecher (79), believe that a non-specific form of linitis plastica may follow a chronic alcoholic gastritis.

7. *Syphilis.* Lues has been recorded in the history of a small percentage of contracted stomachs. In our medical clinic at the State University Hospital, Iowa City, it was only discovered three times among 11,700 medical cases up to the year 1923 (Gatewood and Kolodny (49)). A review of these cases has been made by Hemmeter and Stokes (63) and more recently by Hartwell (58), Böhm (7), Schlesinger (118), and Brunner (16). Graham (quoted by Luria (87)), Hausmann (59), and Hirschberg (64) are of the opinion that syphilis is the most important cause of this rare condition. Hartwell (58) could find up to the year 1925 only twenty-five cases of syphilis of the stomach which had been proven by histological study, and pointed out the fact that many cases which had been diagnosed as syphilis, because of a positive Wassermann and X-ray findings, were later proven to be cancer. While it is true that syphilis of the stomach may lead to fibrosis of the entire organ, it is usually of a more irregular, deforming type and more often confined to the pyloric region, and in our experience is always in association with other evidence of visceral syphilis, particularly of the liver or aorta. Faroy (40), while admitting the malignant nature of his three cases, suggests that the peculiar tendency to fibrosis may depend upon a syphilitic soil, which he considered was present in his cases. Hausmann (59) believes that many of the cases of 'stenosing gastritis' reported by Boas were due to syphilis. In our series the blood Wassermann was tested in nine patients: it was negative on one

or more occasions in eight, and in one case it was negative once and positive once. In none of the ten was there clinical evidence of visceral syphilis, and in the five patients that were examined *post mortem* there was no syphilitic lesion found in any of the viscera.

8. *Tuberculosis.* Some authorities, as Poncet and Leriche (111), Villiers and Phillippen (quoted by Lyle (88)), believe that tuberculosis plays an important role. However, tuberculosis has been strikingly absent from the protocols of the majority of cases, though the presence of a polyserositis has often suggested that possibility. So far as our ten patients were concerned, there was no history of tuberculosis in the family or previous medical history, though two patients were suspected of tuberculous polyserositis, which suspicion was not subsequently confirmed. *Post mortem*, two patients revealed healed pleural and two healed pulmonary tuberculosis, while only one showed an active tuberculosis of both ovaries.

Pathogenesis

In spite of Brinton's warning that only further careful study of the history and morbid anatomy of more cases than those at his disposal would enable one to make safe conclusions as to the benign or malignant nature of the syndrome, many theories have been advanced, each theory, however, based on a study of too small a series of cases.

Among the many theories, one must mention first that of Brinton (15), that linitis plastica is an advanced stage of simple gastritis: second, that of Fenwick (42), that it is a primary atrophy: third, that of von Sury (142), that it is a result of chronic passive hyperemia due to cardiac decompensation: fourth, that of Huchard (67), who considers arteriosclerosis as the cause: fifth, the theory of Poncet and Leriche (111), Villiers and Phillippen (quoted by Lyle (88)), that it results from tuberculosis: sixth, the suggestion of Hemmeter and Stokes (63) that it is of syphilitic origin: seventh, the theory of Bouveret (10) of lymphatic obstruction.

Wilks (144) advanced the hypothesis that it is a primitive sclerosis of the submucosa, while Garret (48) and Bard considered it a sclerosis secondary to fusiform sarcoma. Bret and Paviot (12) believed that it was the result of an infiltrating epithelioma. Schacher (117) enlarged upon the epitheliomatous origin and considered it a pure epithelioma beginning in the mucosa, infiltrating the gastric walls and causing connective-tissue hyperplasia, which produces epithelial buds. Hoche (65), maintaining the epitheliomatous nature, believed it arose from a cicatrizing ulcer. Similar views were held by Danel, who, however, stressed the cancerous involvement of the regional lymph glands. Hansemann (56), on the other hand, held that many of the so-called scirrhous infiltrations of the stomach are in reality endothelioma. This view was also held by Jungmann, Fick (43), and Ssobolew (125). Garret (48) was one of the first to claim that linitis plastica is a diffuse cancer of the stomach, and supports his belief by the statement that 'in linitis plastica secondary nests have been observed in all parts of the intestine: these could not be attributed to primitive cell nests because they appear, not in the mucosa, but in the cellular or muscular layers and

others on the mesenteric side'. They are due to retrograde invasion of the lymphatics and present a phenomenon identical to the one described by Handley in the breast under the term 'permeation'. Krompecher (79) pointed out that gastro-intestinal sclerostenosis is not merely a disease of the pylorus but is found in the intestines and peritoneum, and that it is a result of a chronic venous oedema caused by cardiac insufficiency and arteriosclerosis, and that the pathological process bears a close relation to scleroderma. von Sury's (142) paper of 1907 summarizes the supposed aetiology of linitis plastica as follows: round ulcer of the stomach, phlegmonous gastritis, chronic alcoholic gastritis, protracted vomiting, irritant poisons, congestion from disease of the heart, lungs, and liver, syphilis, chronic perigastritis, peritonitis and retroperitonitis, and trauma.

As pointed out by Lyle (88), all these theories have only two distinct ideas: one, that linitis plastica is a special affection of an indefinite nature and cause: the other that linitis plastica is a special form of scirrhous cancer. Thomson and Graham (128), as recently as 1913, expressed their opinion that the local type of fibromatosis of the stomach frequently arises from ulceration of the mucosa and suggested that ulcero-fibromatosis is a more accurate term than those commonly in use: they thought that the process in some cases is benign, while in others it is malignant. Lyons (90) admits that various lesions may produce the same thickened stomach described by Brinton as linitis plastica, but he believes that the latter term should be reserved for only those cases in which a small-cell cancer is found, which was true of 80 per cent. of thirty-eight cases diagnosed as linitis plastica by the surgeons at the Mayo clinic. These cases represent the only well-defined group. If this restriction be enforced there would be no necessity for suggesting syphilis, tuberculosis, arteriosclerosis, cardiac insufficiency, and alcoholism as aetiological factors. In the localized pyloric form Maier (91) suggests the possibility of a congenital anomaly, which was later illustrated in a case reported by Tilger (130).

Morbid Anatomy

Krompecher (79), on the basis of heredity, localization, and malignancy, has recognized the following groups of linitis:

I. *Benign*, (1) congenital hypertrophy of pylorus, (2) acquired hypertrophy of pylorus, (3) acquired leather-bottle stomach.

II. *Malignant*, (4) acquired hypertrophy of pylorus, (5) acquired leather-bottle stomach.

Friedenwald and Morrison (47) have slightly modified Wyard's (146) classification of the leather-bottle stomach and accept the following groups:

I. *Carcinoma*, diffuse and local, (A) sclerosing carcinoma or carcinoma plastica (improperly called linitis plastica), (B) other forms of carcinoma.

II. *Fibromatosis*, diffuse and local.

They admit that 'the difficulties encountered in differentiating these varied affections can be best recognized by a study of the individual pathologic process'.

All are agreed that two forms occur: (1) local, and (2) general. In the *localized form*, which is rare, there are indurated plaques in different portions of the stomach. The more common form is found in the pylorus,

where the plaques may be of varying extent, often encircling and stenosing the pylorus (Habershon (53), Boas (6), Tilger (130), Chaput and Pilliet (18), Oettenger and Tourlet (131)). In Germany, Gluge was the first, according to Tilger, to discuss the partial hypertrophy of the pylorus. It seldom leads to dilatation of the stomach, the only exception being the case of Nauwerck (102) and Tilger. The infiltration shades insensibly into normal tissue, but stops abruptly at the duodenum, though in Marcy and Griffith's case (93) the infiltration extended to the duodenal entrance of the common duct. Lyons (90) believes the localized form represents an early stage of the generalized process. Curtis (26) describes the rarer localized forms of the stomach and other portions of the intestinal tract, referring particularly to the cases of de Marignac (32), Henrot, and Cricks, which involved the small intestine, colon, or rectum. Curtis's own case revealed a nodular peritonitis, leading to stenosis of the colon and rectum. We have not seen this localized type.

In the generalized form the stomach may be normal in size, dilated, or contracted, though contraction is the rule, dilatation the exception. In a typical case there is a shrunken, thick-walled tube lying transversely across the epigastrium, resembling a segment of the large bowel or, more figuratively speaking, 'a leather bottle'. The walls may be so rigid that, when the stomach is removed from the body, it does not collapse and maintains its original shape. It is firm in consistency, 'in parts almost cartilaginous, but with the elasticity and resiliency of a large artery' (Martin (94)). The lesion begins at the pylorus and may be confined to this region or to one curvature, from which it extends over a part or the whole of the stomach and occasionally to the duodenum and oesophagus. The pyloric orifice projects into the duodenum, as does the cervix uteri into the vagina. In our series of ten cases, the stomach was found much contracted in six cases and dilated in two: in two cases neither laparotomy nor autopsy was performed. The process had extended to the oesophagus in three and to the duodenum, small intestine, or colon in one case each. The serosa of the stomach has a peculiar dull-greyish colour resembling scarred tissue. On section the gastric wall is greatly thickened and may be six to eight times thicker than normal. However, the layers remain distinct. In the advanced cases all the coats are involved, but the most marked involvement is in the submucosa, subserosa, and serosa. Brinton found the submucosa ten to twenty times its normal thickness, the serosa and subserosa seven to ten times, the muscularis five to eight times, and the mucosa two to three times.

The mucosa is often normal in appearance, or it may be thickened and merged into the adjacent layers. It may be thrown into folds or nodular elevations. Primary atrophy is infrequent and ulceration rare. Nevertheless, in two of our cases ulceration was present near the pylorus. Pilliet (108) has also noted the presence of multiple gastric erosions. On section the knife makes a creaking sound as if cutting through cartilage. The cut section is bloodless and no cancer juice can be expressed. It is an evenly infiltrating

process and tumour formation is uncommon. The regional lymphatic glands are usually small and hard, though they are sometimes enlarged from invasion by the tumour cells. The glands most frequently involved are the gastric and mesenteric groups, though more distant ones, as the pelvic and mediastinal, are occasionally affected. Subacute or chronic peritonitis is present in the majority of cases (Brelet (11) and Curtis (26)). Lymph may be present on the intestinal coils: fibrous adhesions are found: ascites or thickening and opacities are present in the lesser and greater omenta, while white waxy plaques are seen on the parietal and visceral peritoneum, or there is thickening of the retroperitoneal tissues, as described by Hanot and Gombault (55) and Pilliet and Sakorraphos (109), under the term 'retroperitoneal callus'. In our series the great omentum and gastro-hepatic omentum were both involved in seven cases: the gastro-colic in three, the mesentery of the small intestine in three, and that of the colon in one. In one of our series the general parietal peritoneum, and in another the pelvic peritoneum, alone were found thickened. Ascites was marked in two and slight in one other case. In one the cavity was obliterated by fibrous adhesions. Similar lesions are found in the small intestine, colon, and rectum: these usually begin in the mesenteric attachment and suggest a retrograde lymphatic involvement. Bret and Paviot (12) regarded these as of cancerous nature, but Krompecher (79) considered them benign and suggested their similarity to scleroderma. Fibrous areas may be seen over the liver and spleen, and in a case reported by Hanot and Gombault (55) the portal vein was converted into a rigid tube. In one of our cases the process extended up the portal vein and bile-ducts to the hilum of the liver. In only one of our cases was the spleen fibrotic, though in another case it was definitely enlarged, apparently from passive congestion, while in another it was invaded by tumour (Case 7). In our series the liver was free from metastases and normal in all respects, except in one case which showed evidence of passive congestion (Case 3). Cholelithiasis was present in another case. Metastases or extension to the pancreas were present in three cases, and to the left adrenal gland and to the bladder each in one case. In one case there was obstruction to the left ureter with resulting hydronephrosis and in another case the pelvic process had occluded the common iliac veins and had led to an enormous oedema of the lower extremities. In the thorax there was a unilateral effusion in two cases, while in a third case (Case 7) it was moderate and bilateral. In one of our cases (Case 9) there was a bilateral tuberculosis of the ovaries. Janow (71) has called attention to the fact that in women a linitis plastica may be complicated by a bilateral Krukenberg tumour of the ovaries, of which he reports one case: he believed that the ovarian tissue offers the epithelial cancer cells of the stomach an especially favourable soil, and that the association of the two conditions does not suggest a primary multiple tumour formation. The lymphatic glands present chronic inflammatory changes, according to Hanot and Gombault (55), but in some cases cancer metastases (Bret and Paviot (12): Danel).

Histology

The mucosa may be quite normal or there may be evidence of a chronic productive or atrophic gastritis. In the advanced cases there is cystic dilatation of the tubules, constriction of the tubules, and other pressure effects of the infiltrating connective tissue. This fibrous infiltration may cause sclerosis with atrophy and a complete disappearance of all the glandular elements (Osler's case (105)).

The submucosa reveals the most marked and constant lesion, namely, a diffuse hypertrophy of the connective-tissue elements. The bundles of connective tissue form irregular bands, interlacing with one another and surrounding the blood-vessels. The latter may show endarteritis. The resemblance which this tangled interlacement of fibres bears to the weave of sailcloth suggested to Brinton's mind the term ' linitis '.

There is a difference of opinion as to whether the epithelial cells found in the submucosa and muscularis are carcinomatous, or whether they arise from the endothelium lining the normal lymph spaces. However, the majority of pathologists consider these nests to be cancerous. Lyons (90) admits that the small cells with large nuclei have been recognized by nearly all students of linitis plastica, but many, while commenting upon their similarity to epithelial cells, have considered them to be connective-tissue elements. ' The process ', according to Lyons, ' represents a high grade of malignancy meeting with great resistance on the part of the subject.'

In the muscularis there is a combination of hypertrophy and atrophy of the muscle fibres. Bands of connective tissue are seen passing from the submucosa through the muscularis to the subserosa. The subserosa shows a marked connective-tissue infiltration, while in the serosa the endothelial cells are destroyed. The lymphatic glands may show a connective-tissue fibrosis.

Summary of the Pathogenesis and Pathology

Before leaving the subject of the pathogenesis, gross and microscopic anatomy of so-called linitis plastica, we must discuss in detail the more recent developments in our knowledge of this symptom-complex, or disease entity, as the case may be. It has long been known, and is especially stressed by von Rokitansky (140) and Kaufmann (quoted by Donath (33)), that the epithelial cells in scirrhous cancer of the stomach may be reduced to the minimum, or may largely disappear, so that a very careful microscopic examination is required to detect traces of carcinoma. It now appears, through the critical analyses of Bret and Paviot (12), Krompecher and Makai (80), and more recently of Lyle (88), that the great majority, if not all the cases of linitis plastica are atypical cicatrizing fibrocarcinoma. Thus, of 130 cases collected by Lyle, 60 may be classified as scirrhous cancer or in the present group of atypical fibrocarcinoma. The remaining 70 occurred under various circumstances. A considerable group appears to be due to

chronic gastritis with marked contraction and thickening of the whole or of one portion of the stomach: in such cases there appears to be hypertrophy, chiefly of the muscular coat, while the submucosa lacks the extensive overgrowth of a malignant linitis plastica. In many of the reported cases (Schmidt (119), Viti (134), Rosenheim (114), Marcy and Griffith (93), etc.) the gross appearance closely resembled scirrhous carcinoma. In several cases there were signs of old superficial ulcers (Formad (45), Allbutt, Turner (133), Meinel (98)). Many cases would suggest the picture of a polyserositis, and reveal multiple thickenings throughout the peritoneum, small intestines, colon, and rectum (Lebert (81), Marijura, Wilks (144), von Kahlden (139), Gabbi (quoted by Tourlet) (131)). Yet in many scirrhous cases the intestinal lesion is chiefly subserous, and the extensions have passed from the stomach to the omentum and colon. While Krompecher (79) originally attributed his group of gastro-intestinal sclerostenosis to cardiac disease, chronic congestion, oedema, and fibrosis, he subsequently conceded their probable carcinomatous nature. Leith (82) has also described a case of this type as non-cancerous cirrhosis, in which the lesion involved the stomach, ileum, and colon, and in which microscopically there was no evidence of carcinoma, though Ewing (39) considers his microscopical report as somewhat lacking in detail. The difficulty of classifying an individual case as benign or malignant in type is well illustrated by the experience of Curtis (26), who reported his case as benign after studying many sections of the stomach, but later (27) had to confess to his critics of the Anatomical Society of Paris that he had subsequently found a block of tissue which revealed typical cancer cells. This would probably be true of many if not all of the other cases which have been classed as benign, in our opinion.

All students of linitis plastica will, we believe, agree with Ewing (39) when he admits that, in dealing with such an extensive collection of anomalous cases, it is impossible to maintain that any one uniform process is represented. It seems possible that rare cases of chronic gastritis, the scarring from ulcer, late syphilis, peculiar forms of trauma, and atrophying processes, may simulate fibrocarcinoma, but it may be claimed that no well-defined group of cases exists apart from fibrocarcinoma. Krompecher (79) points out that the microscopic study of the older cases, and even of the more recent ones, is open to criticism, since the histology of regressing fibrocarcinoma of the stomach is seldom fully recognized. This author and Makai (80) found nine cases in a series of seventeen which they recognized as disseminated fibrocarcinoma, by the discovery of islands of atypical epithelium, or scanty acini of adenocarcinoma, or groups of cells with mucous degeneration and typical signet-ring nuclei. In other portions of these same tissues they found only cellular-granulation tissue or hyaline areas and cells of undetermined origin, all of which made up the bulk of the sclerotic areas in the remaining eight cases in which no definite signs of carcinoma were present. They, therefore, conclude that all their cases were of identical nature and belong to a group of atypical, disseminated, sclerosing carcinoma.

They are inclined to agree with Meinel (98) that a benign acquired cirrhosis of the pylorus and stomach of the type of linitis plastica does not exist. Ewing's own studies have led to the same conclusion with some modifications. He found every gradation from small-celled diffuse and scirrhous carcinoma with pronounced signs of malignancy, down to over-cellular granulation tissue with overgrowing capillaries suggesting an endothelioma, or hyaline connective tissue with scanty cells of undetermined origin, and even to connective tissue without a trace of atypical cells of any type. As a rule, extensive search reveals some foci of characteristic mucous cells in the submucosa or muscularis. It therefore seems necessary to conclude, in spite of the opinion of such a well-known pathologist as Aschoff (2), that all cases of hypertrophic pyloric stenosis and diffuse cirrhosis of the stomach in adults are atypical fibrocarcinoma. Miscellaneous cases of apparently benign character must be regarded with suspicion. In linitis plastica there appears to exist a peculiar form of gastric cancer, probably occurring in resistant subjects and originating from cells of limited growth capacity, which pursues a chronic course and tends to spontaneous regression of the tumour process but, nevertheless, to the death of the patient.

Symptoms

There may be none referable to the stomach, and the patient may die from arteriosclerosis or cardiac failure. In general, when clinical symptoms are present, they resemble those of the scirrhous type of carcinoma, to which, as it has been shown, it is closely related anatomically.

The *onset* is usually insidious, but has been reported as abrupt in a few cases. There is often an indefinite history of dyspepsia for months or years, until more definite gastric symptoms appear which in turn are followed by severe anaemia, cachexia, and death.

In the *first stage* the symptoms are vague and inconstant, and are best described by the term ' indefinite dyspepsia '. This is gradually replaced by the appearance of a more or less complete anorexia, occasional attacks of vomiting, indefinite gastric pain, and tenderness. In our series pain of some degree was present in eight, vomiting in nine, and anorexia in six patients.

The *second stage*. The vomiting, which is at first inconstant, gradually becomes more frequent and finally is incessant. If the lesion is near the cardia the vomiting simulates regurgitation from an oesophageal stricture; two of our cases noted regurgitation and complained also of some dysphagia. The vomiting is never that of gastrectasis, but rather that of a small rigid organ which is intolerant to the quantity of food rather than the quality of the food ingested. The patient often complains of a sense of suffocation and distension in the epigastrium, partly relieved by vomiting. Loss of weight and strength are prominent features. In Lyons's (90) series of thirty-three cases the average loss of weight was twenty-one pounds. In our series three

admitted to loss of weight but could give no definite figures; one admitted to less than ten pounds loss, three to between ten and twenty, one to more than twenty, and one to more than thirty pounds loss. Peritoneal involvement from extension of the disease process results in constipation, attacks of partial obstruction, marked diarrhoea, and ascites. Constipation was the rule in our series, though one patient did complain of periodic diarrhoea. Ascites and general anasarca may appear early, but as a rule are among the terminal events. A marked ascites occurred in three cases, and a slight one in a fourth patient of our series. Hydrothorax is not an uncommon feature and may be bilateral, as was true in two of our series.

Anaemia is a constant finding, and may in some cases be severe enough to resemble a true pernicious anaemia, which dominated the clinical picture in the cases reported by Nothnagel (103) and by Osler and Henry (105). In our series there was anaemia in nine of the ten cases, of slight grade in six, and of a moderate grade in three. Leucopenia was present in seven and a slight leucocytosis in two cases.

Haemorrhage is rare, owing to the integrity of the mucosa of the stomach; therefore, haematemesis is not common and melaena the exception. Nevertheless haematemesis, which may be due either to congestion or less frequently to ulceration of the mucosa, is occasionally copious. Lyons reported gross haemorrhage from the stomach in only one case. We also noted a gross haemorrhage in one case of our small series of ten: however, one other patient vomited slight quantities of fresh blood, while another noted coffee-ground material in the vomitus. In two other cases there was a more or less profuse melaena, while occult blood was found in the stools of a third patient.

An analysis of the gastric contents, after a test meal, reveals a decrease or, more commonly, a complete absence of free hydrochloric acid. In six of our series, in which test meals were given, the hydrochloric acid was absent in five and was present in only small quantities in one case. However, Lyons found, in the thirty-three cases to which a test meal was given, that eight patients revealed the presence of free hydrochloric acid in amounts ranging between 6 and 32 c.c. of n/10 Na (O.H.). In only two of our cases was lactic acid found.

On *physical examination* a transverse sausage-shaped tumour or, at the least, a sense of resistance is often present, as was true in thirteen cases of Lyle's (88) series and in eight of ours; in two of our series it had been noted by the patient himself. In some cases the tumour is visible as well as palpable in the epigastrium, as was true in five of our cases. The stomach cannot be distended with air or carbon-dioxide gas and will only hold small quantities of fluid. Trousseau (132) noted a sensation of grating conveyed to the palpating hand on deep respiration; no similar observation has been recorded, however.

Jaundice is rarely seen, but occasionally occurs from a constriction of the common bile-duct by adhesions. Again, the presence of extensive peritoneal adhesions may give rise to a picture of intestinal obstruction with

resulting persistent and uncontrollable vomiting followed by death from asthenia.

Radiological

Valuable confirmatory information can, of course, be obtained from the X-ray examination, as was first emphasized by Jonas (72), and later by Sailer (116) and McGlannan (97), and which has been employed with increasing frequency in recent years. G. von Bergmann (136) also stresses its value and his belief in the frequency of the malignant type of the cirrhotic deformity of the entire stomach. He recognizes four types from the X-ray standpoint: (1) those which involve the entire or at least the greater part of the stomach: (2) those of the cardia: (3) those of the body of the stomach, and (4) those of the pyloric region. Lyons does not consider the skiagram diagnostic in the localized form, and insists that the generalized form is similar in all respects to a diffuse scirrhous cancer. Nevertheless, much can be learnt by a careful fluoroscopic examination when either dilatation of the oesophagus, a general lack of pliability of the stomach as a whole, or rapid emptying of the stomach are suspicious circumstances. The skiagram itself will reveal in some a dilated oesophagus (as was true in three of our cases) or duodenum, and in the majority a contracted stomach (nine of our series). Sometimes, however, there may be apparent dilatation of the stomach, which was true of one of our series only (Case 2).

The *terminal stages* are marked by a persistent vomiting, emaciation, and cachexia. The chief clinical characteristic seems to me to be the painless course, characterized by regurgitation of food, progressive anaemia, weakness, and cachexia, and by serous effusions into the pleurae or abdomen or into both, suggesting the picture of tuberculous polyserositis or portal cirrhosis. Only a careful routine examination of the gastro-intestinal tract by the stomach tube and X-rays will reveal the gastric origin of the process.

Diagnosis

Linitis plastica was formerly rarely diagnosed during life and was usually a surprise finding at laparotomy or *post mortem*. Boulton (9), in 1862, reports an intra-vitam diagnosis, but no histological study was made. Horn in 1869 was, according to von Sury (142), the first to make a diagnosis in the living patient. However, the honour of the first clinical diagnosis usually is ascribed to Deguy (30), who in 1896 proved his case by gross and microscopic study. According to McCrae (96), Osler in 1901 diagnosed the second case. Evidently these reports had escaped the notice of Hayem and Lyon (60) in 1903 when they stated that no case had yet been diagnosed during life. von Sury (142) believes that the diagnosis depends more upon the subjective than the objective findings. However, thanks to the X-ray, the majority of cases are now recognized, though unfortunately generally in the late stages. Jonas (72) in 1909 is the first to mention the small size of the stomach, with its upright fundus and absence of peristaltic waves.

Differential diagnosis. An accurate differentiation between the various types of linitis plastica is impossible. The condition has been mistaken for (1) movable kidney, (2) movable spleen, (3) movable transverse colon, (4) portal cirrhosis, (5) pyloric stenosis with ulcer, (6) gastric ulcer with degenerative changes, (7) chronic peritonitis, (8) tuberculous peritonitis, and (9) gastric syphilis.

The benign form is differentiated from the malignant or diffuse scirrhous cancer by (*a*) its longer duration (3–15 years), (*b*) the early age of onset (35 years or more), (*c*) the absence of metastases, and (*d*) the freedom from haematemesis.

Gastric syphilis can be differentiated from the malignant type of linitis by (*a*) the earlier age, (*b*) the history of syphilis or the positive Wassermann reaction, (*c*) the retention of appetite (Böhm (7)), (*d*) the earlier reduction of the free hydrochloric acid (Hausmann (59)), (*e*) the absence of occult blood from the stool (Böhm), (*f*) a possibly characteristic skiagram, (*g*) the presence of other visceral syphilis, particularly in the aorta, liver, or nervous system, and (*h*) the disappearance or improvement of symptoms following antiluetic treatment. Böhm (7), reporting seven cases of the localized type, stresses as diagnostic features the sudden appearance of marked gastric symptoms in young persons, a rapid and marked loss of weight with intractable vomiting but retention of appetite, the presence of a palpable tender tumour, an absence of free hydrochloric acid, a low total acidity and the presence of lactic acid in the test meal, an absence of occult blood in the stools, a circular antrum defect in the skiagram, and a positive Wassermann. Lewald (85) believes that one can often, by a careful X-ray study, distinguish between the simple, the malignant, and syphilitic forms of leather-bottle stomach, though he admits that the cautious roentgenologist will reserve his final diagnosis and merely report to the clinician his findings in detail, stating the three possibilities, (*a*) syphilis, (*b*) diffuse carcinoma, and (*c*) fibromatosis of the stomach. Eisenklam (37) and Bönnig (8) both discuss the diagnosis of the syphilitic Schrumpfmagen, but only the latter admits to the difficulty of excluding a scirrhous cancer. Eusterman (38) and Lewald, in their most recent papers, have added but little to our knowledge of the recognition and differential diagnosis of a syphilitic contracted stomach. We are in accord with Gatewood and Kolodny (49) as well as with Hartwell (58) that ' only those cases of syphilis of the stomach and intestines which have been diagnosed histo-pathologically are absolutely convincing '.

Prognosis

The course of the disease is always long, but the period of observation may be brief. The duration in forty-three cases of the benign form varied from three months to twenty years: the average forty-nine months. In thirty-seven cases of the malignant form the shortest duration was one month, the

longest fifteen years ; the average duration equalled 23·9 months according to Lyle (88). Lyons (90) found in thirty-three cases the average duration of symptoms was twenty-three months, with extremes of fifteen years and five weeks. The disease is uniformly fatal unless treated surgically.

Treatment

The medical management of this condition is, at the best, palliative. Rest, fresh air, a mild and bland nutritious diet, nutrient enemata, gastric lavage, paracentesis of the pleura and peritoneum, opiates and cardiac stimulants, prolong life and render the patient's final weeks more comfortable.

Surgery, more especially in the early stages, offers more promise of palliation or even cure. The various surgical procedures that have been reported are (*a*) total gastrectomy (three cases), (*b*) partial gastrectomy (thirteen cases), (*c*) gastro-enterostomy (nine cases), (*d*) pyloroplasty (one case), (*e*) gastrostomy (two cases), (*f*) jejunostomy (four cases), and (*g*) manual dilatation (one case). As one might expect, even the surgical results are not very encouraging. Nevertheless, Roux (115) and Sheldon (122) have each reported cases which were well three and one-half years after a gastro-enterostomy, and von Eiselberg (138) one patient cured by jejunostomy, while Gayet and Patel's (50) patient survived a total resection for the malignant type of linitis plastica.

Conclusions

1. After careful study of the many reported cases of linitis plastica, and from our own personal experience, we are forced to the conclusion that the majority of cases belong to the sclerosing type of carcinoma.

2. While we are not in a position to deny the existence of a benign form (the so-called fibromatosis), we believe that many of the reported cases have not been submitted to a careful enough histological scrutiny to exclude a malignant process.

3. While syphilis may be an exciting factor in a certain number of cases, we suggest that in the majority of the so-called syphilitic leather-bottle stomachs there has been a secondary invasion by cancer cells.

4. The clinical picture of every case, whatever be its aetiology, is that of a rather chronic form of cancer of the stomach.

5. An early exploratory laparotomy should be carried out and, where possible, some radical form of surgical procedure undertaken.

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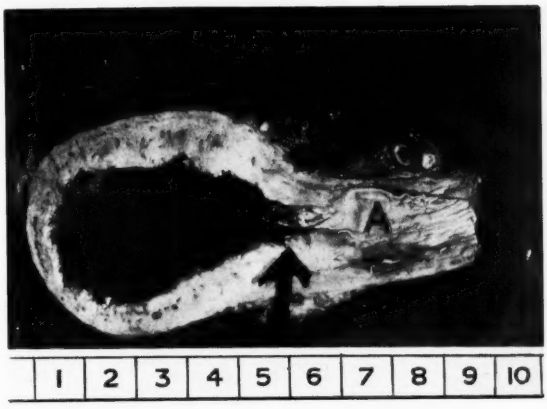


FIG. 1. Case 10. Longitudinal section through cardia to show oesophagus 'A' and stomach. Extensive tumour infiltration

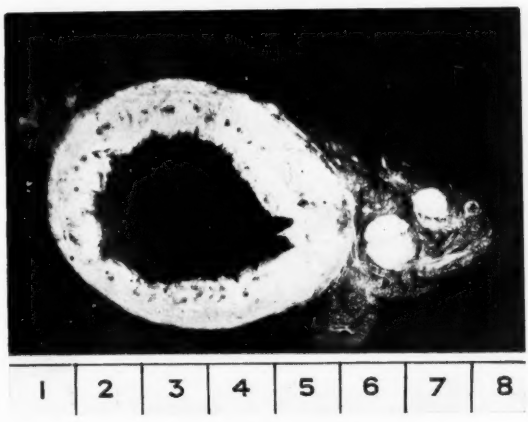


FIG. 2. Case 10. Transverse section through fundus with perigastric lymph nodes. The latter are displaced by carcinoma. Stomach shows extensive infiltration with carcinoma

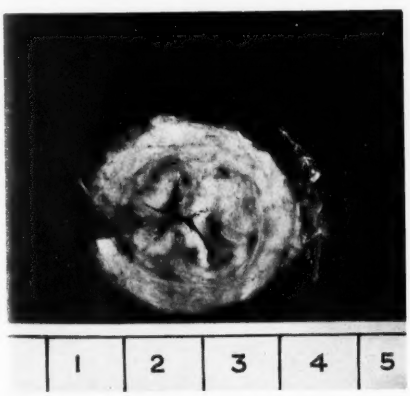


FIG. 3. Case 10. Transverse section through pyloric end of stomach. Note extensive tumour infiltration with very small lumen of stomach

FIG. 4. Case 10. Longitudinal section through pylorus and duodenum. Note extensive infiltration of pylorus with tumour

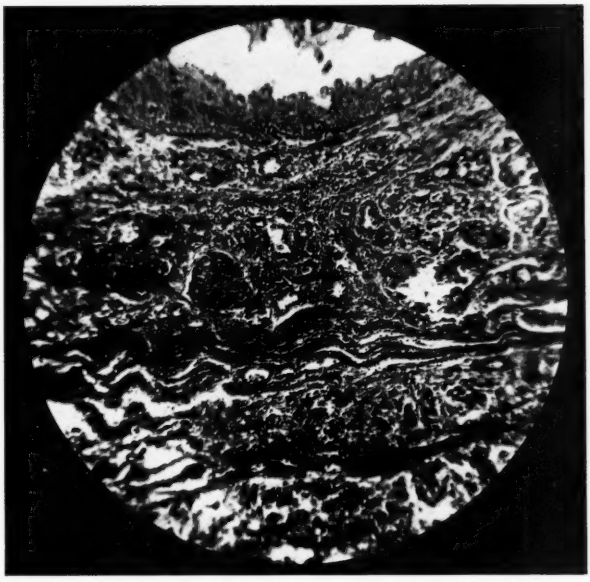


FIG. 5. Case 10. Extensive infiltration of submucosa of stomach. The mucous membrane is not infiltrated

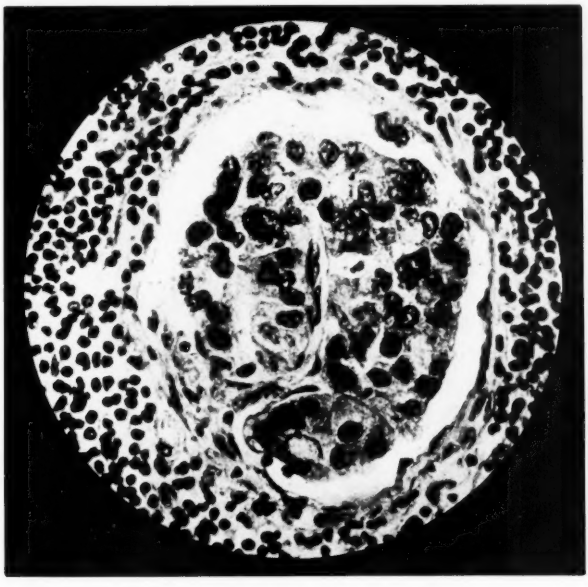


FIG. 6. Case 10. Lymphatic vessel in submucosa distended with tumour cells and surrounded by lymphocytes

616–008.851
616–008.816

THE ERYTHROCYTE SEDIMENTATION TEST
A CLINICAL AND EXPERIMENTAL STUDY[1]

By A. C. REES WALTON

With Plate 15

THIRTEEN years have now elapsed since Fahraeus (1) first published his discovery of a decrease in the suspension stability of citrated blood obtained from pregnant women. This 'test' for the pregnant state at first seemed to offer great promise and, naturally, attracted a good deal of attention because the need of a sure indication of early pregnancy had long been evident. As the test became more widely used it soon became patent that many other conditions besides pregnancy could cause an increased sedimentation rate—for example, acute and chronic infectious processes and malignant new growths.

When, in March, 1927, I commenced to investigate the value of the sedimentation test (subsequently referred to as S. T.) I was confronted by an immense wealth of literature upon the subject. The amount of work already done was sufficient testimony to the enthusiasm which this serological test had aroused, but it soon became apparent from the number of contradictory reports and the multiplicity of methods that some fallacies existed. It seemed rather a striking fact that, in spite of the amount of research which had been done during the preceding nine years, the value of the test had been neither proved nor disproved. At the present day the position is still much the same: publications are still appearing, some condemning and others upholding the value of this reaction. When, therefore, this research was initiated it was determined to tackle the problem from an unbiased point of view and to investigate the fundamental principles of the S. T.

Gradually, as experimental data began to accumulate, an original technique was evolved in which were eliminated several factors of error which will later be shown to account for many of the conflicting results which have been published. Investigations were made as to the causes of the modifications of the sedimentation rate (subsequently referred to as S. R.), thence to its application in the spheres of clinical medicine and experimental biology. The total number of experiments has not been calculated but they

[1] Received March 23, 1932.

run into several thousands; there are recorded, however, 600 sedimentation tests upon blood taken from 460 patients and upwards of 1,000 experiments upon animals.

It is not possible in the scope of this communication to enter into a description of the numerous methods employed by other workers. Suffice it to say that their results are not comparable, owing to their diversity of principle. The most important methods are those described by the following authors: Fahraeus (2), Linzenmeier (3), Westergren (4), Katz (5), Lundgren (6), Gram (7), Rourke and Ernstene (8), Plass and Rourke (9), Balachowsky (10), and Cutler (11), and of these only Gram, and Rourke and Ernstene, make any attempt to correct the S. R. for fluctuations in red cell content.

A Critical Study of Experimental Conditions

(a) *The sedimentation tube.* Under this heading we include diameter, length, and angle of inclination of the tube. It was found that, when the tube is of very fine diameter, the upper layer of red cells is ill defined, due to their irregular fall, and a tube of less than 2 mm. internal bore should, therefore, not be used. The most constant and even results have been attained in tubes whose length was 6 cm. and whose internal diameter was 6 mm. The sides of the tube must be parallel and the lower extremity flat. The tube must be held quite vertical during the process of sedimentation, for Lundgren (*loc. cit.*) showed experimentally and Ponder (12) demonstrated theoretically that the S. R. in inclined tubes is much increased over that in vertical tubes. In fact, in a 200 mm. column, a divergence from the perpendicular of only 7·5 degrees is enough almost to double the S. R.

(b) *Influence of the red cell count.* This factor has been largely neglected, and it is only during the last year or so that efforts have been made to correct for fluctuations in the red cell count. Fahraeus (*loc. cit.*), Bönniger and Herrmann (13), and Hubbard and Geiger (14) have mentioned that the S. R. is faster in anaemic blood, whilst Cooper (15) and Rubin (16) state that the red cell factor plays no appreciable part. However, in 1929, Gram (17) and in 1930 Rourke and Ernstene (*loc. cit.*) described methods for correcting the S. R. upon a fixed standard. During early experiments, using various dilutions of red cells in their own plasma, I was soon struck by the fact that the erythrocyte content was a most important factor and that, in order to compare the S. R. of different blood samples, it was necessary to keep the number of red cells constant. To this end an arbitrary figure of 5,000,000 red cells per c.mm. was chosen and a tube containing blood of this concentration was set up in every case. Since March 1927 this rule has been followed, until lately a simplified modification has been utilized. In fact for the first 400 cases a series of 5 tubes was always set up, containing a diminishing content of red cells from 5,000,000 down to 1,000,000 red cells per c.mm. A simple method of calculating the necessary dilutions was found in an article by Blacklock (18). As applied

to the dilution of the blood the following example may be quoted: Initial red cell count 5,400,000 per c.mm.; the million figure is noted and a similar quantity of blood in cubic centimetres (i.e. 5 c.c.) is placed in a suitable tube; to this blood is added a quantity of plasma (obtained from a previously centrifugalized sample of the same blood) which is represented in fractions of a cubic centimetre just as the red cell count figure below the million cipher is represented in fractions of a million. Thus to 5 c.c. of blood is added 0·4 c.c. plasma, and this tube now contains 5·4 c.c. of blood at a concentration of 5,000,000 red cells per c.mm. It is but a simple matter to redistribute this into five sedimentation tubes, each containing 1 c.c. of blood in descending concentration. Working upon the same principle we can concentrate anaemic blood, and by suitable removal of plasma we may obtain at least 1 c.c. of blood at a concentration of 5,000,000 red cells per c.mm. It is almost unnecessary to add that, before and after each addition or subtraction of plasma, careful mixing of the erythrocyte suspensions must be performed. That this method is satisfactory I proved on very frequent occasions, by checking and rechecking the blood count at different stages in the process. It was evident from the very first that even small variations in the red cell content made a great difference in the S. R., for an acceleration in the latter occurs progressively in parallel with the increasing dilution.

Examples

Case 1. Normal. Red cell count = 4,680,000 per c.mm.

Tube No.	Contents.	S.R. in 1 hour.
5	5,000,000 red cells per c.mm.	1 mm.
4	4,000,000 „ „ „	6 mm.
3	3,000,000 „ „ „	10·5 mm.
2	2,000,000 „ „ „	20·0 mm.
1	1,000,000 „ „ „	27·5 mm.

Case 18. Carcinoma of cervix uteri. Red cell count = 4,270,000 per c.mm.

Tube No.	Contents.	S.R. in 1 hour.
5	5,000,000 red cells per c.mm.	9·0 mm.
4	4,000,000 „ „ „	13.5 mm.
3	3,000,000 „ „ „	20·0 mm.
2	2,000,000 „ „ „	23·5 mm.
1	1,000,000 „ „ „	27·5 mm.

These examples clearly show what a notable influence the number of red cells has upon the S. R. in any particular case. On many occasions an individual, who was normal clinically, has shown a somewhat increased S. R., but when the cell count, which was in the neighbourhood of 4,000,000, was brought up to the 5,000,000 concentration, a much slower and normal S. R. was registered. Comparison of a large number of such results brought to light the interesting fact that, in the higher dilutions, relatively little margin of difference was to be found between normal and pathological cases, whilst in the 1,000,000 tube a S. R. of 27·5 mm. was nearly always recorded

in the slowest, as in the fastest, sedimentation specimens. On the other hand, the most uniform sedimentation and the greatest difference between normality and abnormality was always observed in the 5,000,000 tube. Furthermore Hesser (19) has shown that agglutination and rouleaux formation (upon which the speed of sedimentation depends) occur best in a high concentration of red cells. Dilution of the blood led to a diminished degree of this agglutination phenomenon. Such a feature is well seen if columns of blood of different concentrations are observed during the process of sedimentation. Whereas in the 5,000,000 tube a well-defined upper margin of the red cell mass always obtains, in the higher dilutions a red haze of loosely attached and non-agglutinated red cells is seen above the main column—rendering an accurate reading of sedimentation height impossible.

As a routine basis for comparison, therefore, it was decided to record the sedimentation height in a tube containing 1 c.c. of blood at a concentration of 5,000,000 cells per c.mm.

(c) *Influence of anticoagulant.* The most widely employed anticoagulant is sodium citrate solution in concentrations varying from 2–5 per cent. It is fairly obvious that when a solution of sodium citrate is added to the blood it should be employed in such strength and quantity that it will exert no appreciable osmotic influence upon the erythrocytes—a point which has only once been emphasized, and that was by Westergren. Therefore an isotonic solution should be utilized and added in minimal quantity, so as to interfere with the S. T. as little as possible. I found that 1 c.c. of an isotonic solution (i.e. 3·8 per cent.) was quite sufficient to prevent 9 c.c. of blood from clotting, whereas most authors have employed double that amount of citrate. If more than this is used, the agglutination properties of the plasma may be reduced (Hesser). Many parallel experiments were made, using various coagulants, such as potassium oxalate crystals, hirudin, heparin, and novarsenobillon, but sodium citrate solution was found to be the most practicable.

(d) *Influence of temperature.* The room temperature at which the S. T. is performed must be taken into account. It was noted that a much greater speed of fall was obtained when a sedimentation tube was placed in an incubator at 37° C. than when a similar tube of blood was allowed to sediment at room temperature (19°–23° C.). In 1928 Gordon and Cohen (20) published an account of a similar series of experiments. The optimum room temperature is 19°–23° C.; above or below this marked deviations are found—deviations which may lead to erroneous interpretations of the S.T.

Personal Technique[2]

The first essential is that the glass tubes, pipettes, and syringes should be kept scrupulously clean and dry. A flask of fresh, sterile solution of sodium

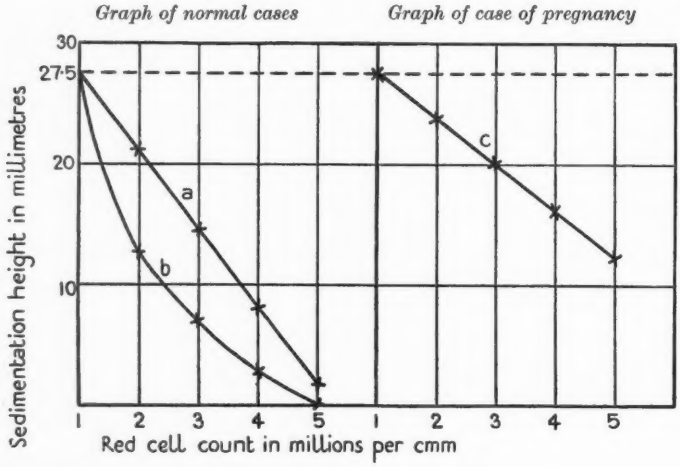
[2] A more detailed description of the technique is now in the press (54).

citrate (3·8 per cent.) is kept tightly corked so as to prevent evaporation, and thereby concentration. The actual sedimentation tubes are 6 cm. long, 6 mm. in internal diameter, and the bottom of the tube is flat. A mark is cut on the glass at a height of 32·5 mm. from the base, this mark indicating a content of 1 c.c. Lately I have used tubes graduated in half-millimetres, but for some time I found it quite simple to measure the height of sedimentation with a flat metal scale. A special rack was designed so that the tubes should be held vertically during sedimentation. This rack contained a series of holes in its upper platform and corresponding slots in the base, so that the tubes should fit snugly when inserted. For the purposes of my investigation I had for a long time set up a series of five sedimentation tubes containing blood in descending concentration from 5,000,000 to 1,000,000 red cells per c.mm., and in such instances 10 c.c. of blood was necessitated. Later, however, it was found that 4–5 c.c. of blood would suffice, so that one tube should be obtained with a content of 5,000,000 red cells per c.mm. By the usual method 4·5 c.c. of blood is withdrawn from an antecubital vein, taking great care not to produce an unnecessary degree of venous stasis, because otherwise, in a rapidly sedimenting blood, some erythrocyte fall *in vivo* will occur. This specimen is rapidly introduced into a tube containing 0·5 c.c. of the citrate solution, and the two fluids are intimately mixed. A red cell count is then made so that we shall know approximately how to divide the specimen for dilution or concentration. It is most frequently found expedient to place 2 c.c. into a small tube and centrifugalize the other 3 c.c. in order to obtain plasma with which to dilute the sample to be tested. The object is to obtain at least 2 c.c. of blood which will have a content of an even million figure in red cells. From this suspension we can readily transfer to the sedimentation tube, after suitable dilution or concentration, 1 c.c. of blood which shall contain 5,000,000 red cells per c.mm. When this is obtained the tube is inverted several times, and rotated about its long axis to produce an even suspension; bubbles on the surface of the blood are removed by touching with a heated glass rod, and sedimentation is allowed to proceed.

At the end of an hour the sedimentation height is read, and then, if desired, the specimen may be centrifugalized for half an hour to obtain the corpuscular volume percentage from which the volume index of the erythrocytes can be calculated. This photograph (Plate 15, Fig. 1), depicts better than any written description the influence upon the S. R. of the concentration of red cells. A much more rapid rate of fall is attained in the more dilute specimens, quite a marked difference in the 4,000,000 as compared with the 5,000,000 tube. An average series of figures for the S. R. in the five tubes for normal blood is as follows:

	Male.	Female.
No. 5 tube containing 1 c.c. of blood with 5,000,000 cells per c.mm.	2·0	3·5
No. 4 tube containing 1 c.c. of blood with 4,000,000 cells per c.mm.	8·0	9·5
No. 3 tube containing 1 c.c. of blood with 3,000,000 cells per c.mm.	14·5	15·5
No. 2 tube containing 1 c.c. of blood with 2,000,000 cells per c.mm.	21·0	21·5
No. 1 tube containing 1 c.c. of blood with 1,000,000 cells per c.mm.	27·5	27·5

Now some individual variation occurs, the normal figure for the 5,000,000 tube for men being found to lie between 0·0 mm. and 5·5 mm., with an average of 2·0 mm. Females show a somewhat faster rate of fall, and the normal values are found to lie between 0·0 mm. and 5·5 mm., but the average is 3·5 mm. More range of variation is found to occur between a normal and a pathological case on comparison of the 5,000,000 tubes. It seems that when blood is so dilute that only 1,000,000 red cells per c.mm. are present, no difference can be found to exist in the S. R. of normal and abnormal specimens. At the end of one hour the erythrocytes in normal blood at such dilution fall through a distance of 27·5 mm. In equivalent concentration, erythrocytes from a pathological case traverse a similar distance. Sometimes the height recorded in such a specimen would be 28·0 mm., but the difference is so slight as to be almost negligible.



Example: (*a*) Average normal graph.
(*b*) Graph of extremely slowly sedimenting blood.
(*c*) Very rapidly sedimenting blood from a case of pregnancy.

This fact is well seen if the following photograph (Plate 15, Fig. 2) is compared with the previous one. It is a sample of blood taken from a pathological case where the S. R. was much more rapid than in the former cases. The photograph was taken at the end of one hour's time from the point at which the tubes were set up for sedimentation to take place.

After extensive observations of this nature, I came to the conclusion that it was possible to estimate the S. R. of any given concentration of blood if the S. R. of a known concentration were obtained.

When S. R. values were plotted upon a graph, with the blood count values as abscissae and the S. R. as ordinates, a curve was obtained which almost described a straight line. In very slowly sedimenting blood the curve bends with the convexity downwards, and the more rapid the S. R. the more nearly straight is the line.

From a consideration of these curves it will be seen that if we know the S. R. in a tube containing, say, 5,000,000 corpuscles per c.mm., the S. R. at any given concentration of blood may be found by plotting a graph and drawing a straight line between the known figure and the 27·5 mm. mark. By producing a line from the red cell count line to cut this straight line, we read off the S. R. for the blood count desired. Vice versa, if we have a tube of blood at a concentration of, say, 4,500,000 cells per c.mm., a straight line is drawn upon the graph joining the S. R. figure for this count and the 27·5 mm. mark. By producing this line we can obtain the theoretical S. R. of a specimen of blood containing 5,000,000 cells.

It is upon this graphic method that I have based a simple procedure for obtaining the S. R. in an individual by taking merely 1 c.c. of blood instead of the normal 10 c.c. This is the method that has been aimed at by others, particularly Gram, but as they were not conversant with the simple concentration and dilution principles, they were unable to work out the S. R. for any given number of red cells. I have employed the method largely, and am convinced of its utility and exactitude, as far as one may apply such a term in a test such as this. The procedure is as follows: A small dry 1 c.c. 'Record' syringe is taken and 0·1 c.c. of the usual sodium citrate solution sucked into it. A tourniquet is placed upon the arm, and blood withdrawn until exactly 1 c.c. of citrated blood is obtained. The contents are evacuated into the ordinary sedimentation tube, which is agitated so as to mix thoroughly the blood and citrate. A haemocytometer pipette is introduced into the suspension and blood enough withdrawn for a red cell enumeration, whereupon sedimentation is allowed to proceed in the usual way. In this manner a large number of specimens can be set up and their S. R. estimated. When the blood cells have been counted, the S. R. at the end of one hour is plotted on the graph opposite the corpuscle number of that blood. From this it can readily be estimated what the S. R. would be if the red cell count were 5,000,000. In some cases it is advisable to utilize a small quantity of blood only; for example, it may be necessary to repeat the S. T. at frequent intervals during the course of a certain disease such as pulmonary tuberculosis, or when performing the S. T. upon infants, and the longitudinal sinus route is chosen, it is preferable to employ as small a quantity of blood as possible. In such cases the method just described is admirable. However, when the erythrocyte count is below 3,000,000, the modified method is not so accurate, more particularly in the quickly-sedimenting specimens, therefore it is urged that with red cell counts below 3,000,000 the blood should be concentrated so that a tube of 1 c.c. may contain 5,000,000 red cells per c.mm.

The Normal S. R. and its Modifications in Physiological States

(1) *Influence of age.* The sedimenting property of the blood varies, to some extent, with age. No sedimentation is found at the end of one hour in the blood of a new-born infant, although the maternal blood at that time

shows a marked decrease of suspension stability. This is a finding which is universally accepted, but opinions differ as to the S. R. from infancy to puberty. György (21), along with Fahraeus (*loc. cit.*) and others, have agreed that the blood of the new-born infant shows the least sedimenting properties, but it is reported by Dehoff (22) that during the first month of life there is a very rapid S. R. which diminishes during infancy until the normal adult figure is attained towards puberty. Personal observations on a few infants contradict the latter view, the following results being recorded:

Case No.	Age.	Diagnosis.	S.R. in 1 hour in 5,000,000 tube.
157	2 days	Icterus neonatorum	0·0 mm.
188	3 „	Spina bifida. Icterus neonatorum	0·0 mm.
159	4 „	Icterus neonatorum	0·0 mm.
168	8 „	Normal: no icterus	0·0 mm.
164	7 weeks	Marasmus	1·5 mm.
180	15 „	Marasmus	0·0 mm.
211	16 „	Marasmus	0·0 mm.
197	2½ years	Rickets with healing fractures	3·25 mm.
194	4½ „	Narcolepsy	0·0 mm.
138	5 „	Atonic colon	3·5 mm.
144	5 „	Same—re-done at a later date	3·5 mm.
203	6 „	Normal	2·0 mm.
205	6 „	Normal	5·0 mm.
209	7 „	Renal calculus (afebrile)	5·0 mm.
170	8 „	Normal	0·5 mm.
201	9 „	Hemihypertrophy	5·0 mm.
171	9 „	Normal	3·5 mm.

These figures for the S. R., assessed upon a standard basis of red cell concentration, show that at no time before 9 years of age, at any rate, is the adult figure surpassed. Even up to 4 months of age the blood suspension stability is very high.

With regard to the figures for normal adults, males (thirty cases) and females (twenty-eight cases) must be taken separately, for the latter show a slightly higher rate of sedimentation. In no proven normal adult male was a S. R. figure of more than 5·5 mm. recorded, and similarly for females 5·5 mm. was the highest figure in the proven normals. Two females, however, were included in the list as normal who gave figures of 6·5 mm. and 6·0 mm., respectively. The first case had an ovarian cyst and the second suffered from migraine, conditions which in themselves do not lead to an acceleration of the S. R., but nevertheless it is doubtful if these cases should be considered as normal when the sedimentation rates are compared with other strictly normal figures.

Table of Normal Adult S.R. Figures

Author.	Male.	Female.
A. C. R. Walton	0–5·5 mm. (av. 2·0 mm.)	0–5·5 mm. (av. 3·5 mm.)
Kreindler and Popper (23)	3–6 mm. (av. 4·5 mm.)	4–8·0 mm. (av. 6·0 mm.)
Westergren	1–3 mm.	5–7 mm.
Gram (24)	2·5–6·0 mm. (av. 3·9 mm.)	2·5–7·25 mm. (av. 4·7 mm.)
Fahraeus	3·3–10·0 mm.	7·4–13·0 mm.
Linzenmeier	600 minutes	200–350 minutes

(2) *Influence of sex.* From the foregoing table it is obvious that the S. R. in the female is slightly more rapid than that in the male. Moreover, in the female sex, certain physiological states, such as menstruation and pregnancy, are capable of influencing the S. R. to some degree.

(a) *Influence of menstruation.* The S. R. was estimated several times upon each of six women at different phases during the menstrual cycle. It was found that the red cell count remains constant throughout, but that the S. R., on the contrary, fluctuates in a rhythmical manner, thereby coming into line with other well-recognized modifications of the female organism, such as, for example, the basal metabolic rate. In some instances the patients were suffering from pulmonary tuberculosis, and in these an acceleration of the S. R. was observed during the short premenstrual phase which corresponds with the slight rise in temperature and metabolic rate so frequently noted in such conditions. During the menstrual flow a sudden diminution of S. R. occurs, to be succeeded in the later post-menstrual, or resting interval, by a slow rise in rate until the acme of sedimentation speed is reattained in the premenstrual phase. In normal individuals this fluctuation is of little importance from the point of view of differential diagnosis as the maximum figure attained is not above the normal for women. However, if the progress of a pathological lesion is being recorded by means of the S. R., then the slight but definite fluctuations due to the menstrual periods should be taken into account.

(b) *Influence of pregnancy.* Personal observations include a series of thirty cases of pregnancy, of which twenty-three may be considered as normal, and the remainder were complicated by eclampsia or other diseases. It was found that, although the pregnant state tends to cause an acceleration of the S. R., none is evident until the 10th to 12th week, and even at a later date than this a normal rate may still persist.

(3) *Influence of digestion.* In normal individuals the ingestion of food is followed by no change in the S. R. as a rule, but sometimes a very slight retardation may be found.

Modifications of the S. R. in Pathological Conditions and the Application of the S. T. to Different Branches of Medicine

Following the introduction by Fahraeus in 1917 of the S. T. as a diagnostic agent in pregnancy, numerous workers seized the opportunity of exploring various branches of medicine by means of this new test. Great was the enthusiasm displayed by these early observers; but, when the value of the reaction was put to the keen test of clinical application, the early enthusiasm abated somewhat, and the speculative stage gave place to a more considered and hesitant judgement. The limitations of the procedure gradually became recognized and its applications more specialized.

Most febrile states are accompanied by an accelerated S. R., as, indeed,

occurs in every case where active tissue destruction is taking place. However, an accelerated S. R. is not by any means always accompanied by a rise in temperature. Such conditions as cancer and chronic tuberculosis may be afebrile and yet show a very rapid S. R.

While the S. R. is not a specific diagnostic agent for any determined disease, it is able to distinguish a normal individual from one in the early stages of some latent pathological process, even in the absence of fever and leucocytosis. In this way we may employ the test in early diagnosis and in the differential diagnosis of many conditions, but it must at all times be regarded only as a clinical aid that must be used intelligently with the remaining clinical picture, being interpreted only after excluding physiological factors which are capable of producing an increased S. R.

In its role as prognostic agent the test has probably played the most important part, for the effect of treatment can be rigidly observed and a vigilant eye can be kept on the convalescence. Naturally tuberculous lesions have afforded the greatest scope for this latter employment of the S. T., and most sanatoria now utilize the procedure as a routine.

We will proceed to review the results obtained from an investigation of the S. T. in the various branches of medicine, surgery, and gynaecology, emphasizing from time to time various interesting data found during the course of this work, and comparing results obtained with those published by others. A great deal of time was spent on the application of the S. T. to the study of tuberculosis, but the report is too lengthy for inclusion here.

(a) *Gynaecology and obstetrics.* There are a great many authors who strongly uphold the utility of the S. T. in gynaecology, and yet others, having found a number of anomalous results, deny that the test is of any practical value. Baer and Reis (25) in 1925 and again in 1926 (26) published their experiences in the field of operative gynaecology, and concluded that the S. T. was of great value in determining the presence or absence of infection in the body, that the S. R. was directly proportional to the virulence of infection, that the S. T. was a more delicate prognostic index than the leucocyte count or temperature curve, and that the test could be utilized as an aid in determining the safe time for operative interference in pelvic inflammation. Schmitz (27) in 1926 and Williams (28) in 1927 contradicted these findings. Schumacher and Vogel (29), Nitschmann (30), Falta (31), Polak and Tollefson (32), and many others are convinced of the value of the S. T. in gynaecological conditions. In each of the latter two publications the results are based upon an examination of 1,000 sedimentation tests. My own conclusions are based upon eighty investigations made when House Surgeon in the Gynaecological Department of the General Hospital, Birmingham.

The following conclusions were established:

(i) The normal pregnant state is accompanied by a rapid S. R. which appears at the 10th to 12th week of gestation and thereafter increases still further. During the puerperium a gradual diminution in the S. R. occurs until a normal figure is reattained from the 14th to 20th day. The S. T. is able

to give warning of the onset of puerperal morbidity by the finding of an increasing S. R. long before clinical signs are manifest.

(ii) Non-inflammatory diseases of the pelvic organs, excluding malignant growths, give a normal S. R. Benign tumours, unless complicated by torsion or necrosis, cause no acceleration in the S. R. Hence the S. T. may be employed to distinguish a simple ovarian cyst or uterine fibroid from the uterine enlargement due to pregnancy after the 12th week, and extra-uterine pregnancy can be distinguished from pelvic inflammatory disease.

(iii) So sensitive is the S. T. that it is able to detect a focus of inflammation in the pelvis in spite of a normal temperature and leucocyte count, so that, when the vaginal examination is equivocal, recourse to the serological test will repay the extra trouble. Acute inflammatory processes and malignant growths cause an accelerated S. R., but a normal S. R. is usually found with even severe ulceration of the cervix uteri, whereas a carcinoma of the cervix almost invariably increases the rapidity of sedimentation.

(iv) A clean operation is sufficient to increase the S. R. by the resorption of katabolic products from the wound area. The S. R. returns to normal in 10 to 16 days after operation just as after successful extirpation of an inflammatory focus, but the finding of a rapid S. R. after this time, on repetition of the test, will presage certain degrees of post-operative morbidity—even haematomata and infection of the wound being sufficient to accelerate the S. R.

(b) *Surgical affections.* Fractures and wounds, even when aseptic, cause a moderate acceleration of the S. R. The incised wound resulting from an operation usually leads to an accelerated S. R. due to resorption of products of tissue destruction, and when healing by first intention takes place a slow diminution of the S. R. ensues, normality being reached when the wound cicatrizes from the 10th to 16th day.

Acute and chronic infectious processes are accompanied by rapid sedimentation, and the S. T. in chronic conditions will be found to be a far more reliable index than the temperature curve or the leucocyte count.

Acute osteomyelitis, lymphangitis, and similar conditions, cause an early acceleration of the S. R., whilst chronic infections such as tuberculosis, actinomycosis, and syphilis, bring about an increase in the S. R. according to their state of activity and virulence. Two cases of actinomycosis gave very rapid S. R. figures.

Case No.	Remarks.	Red cell count.	S.R.	Colour index.	Volume index.
108	A corn merchant with a pericaecal granulomatous mass and a discharging sinus	4,000,000	12·5	0·96	1·02
109	Sinus formation after an operation for acute appendicitis: streptothrix isolated from pus	4,190,000	16·0	0·68	0·85

Benign tumours, renal calculi, arthritis deformans, and bony deformities, such as coxa vara, Perthe's disease, or pseudo-coxalgia, give a normal S. R. Malignant tumours, on the other hand, usually augment the S. R.

In orthopaedic surgery the S. T. has given very satisfactory results, especially as a prognostic agent, and as an index of the possibility of mobilization of joints. Not the least important in this branch of surgery is the valuable aid afforded by the S. T. in the differential diagnosis of pathological conditions of the joints.

The most rapid S. R. is given by a tuberculous arthritis, but several types of acute arthritis give a rapid S. R., for example, the rheumatic, gouty, and gonococcal arthritis. The latter show a relatively rapid return to a normal S. R., whilst acute polyarticular rheumatoid arthritis shows a rate of sedimentation which continues at a higher level with a gradual diminution in rate in the quiescent periods. Osteoarthritis, on the other hand, does not augment the S. R., being a non-infective condition.

Raszeja (33) has employed the S. T. in orthopaedic surgery on a considerable number of cases, and finds the S. T. very trustworthy in the diagnosis of chronic bone pathology in young individuals. He particularly studied tuberculosis of bones with special reference to prognosis, and came to the conclusion that the rapidity of sedimentation depends upon the intensity of the pathological process and the gravity of the infection. The most rapid S. R. figures are given in Pott's disease, softenings, and abscess formation.

In the differential diagnosis between a tuberculous arthritis and pseudocoxalgia, coxa vara, or osteoarthritis, the S. T. proves of value; similarly an infectious arthritis may be distinguished from a foreign body in the joint, flat foot from tuberculous implication of the tarsus, and a simple intercostal neuralgia from a tuberculous rib. A few illustrative cases are the following:

Case No.	Diagnosis.	Red cell count.	S.R.
221	Acute rheumatoid arthritis of finger joints	4,570,000	7·0
229	Chronic rheumatoid arthritis of vertebral joints—slight activity	4,000,000	7·0
235	Lumbago	4,790,000	1·75
38	Chronic osteoarthritis	4,550,000	3·0
320	Chronic tuberculous spondylitis with very slight activity, clinically and radiologically	4,030,000	8·5
104	Active tuberculous spondylitis with psoas abscess	5,250,000	14·0
151	Caries of spine	5,700,000	13·0
120	Chronic osteomyelitis—febrile	5,140,000	16·0

In urological surgery the S. T. may be utilized in the differential diagnosis of renal calculus from infections of the kidney, especially renal tuberculosis, unless a gross infection accompanies the calculus. Tuberculous disease of the urogenital tract, if active, increases the S. R., but a latent focus may be brought to light by measuring the S. R. before and after the injection of a minute dose of tuberculin.

The above statements agree with those of Coeytaux (34), Gram (17), and Pijper and Russell (35).

Gonococcal infections of the urethra, prostate, and epididymis do not accelerate the S. R. unless chronic abscess formation supervenes. The following are examples showing the S. R. in renal lithiasis:

Case No.	Red cell count.	S.R.
500	5,200,000	0·5
125	5,130,000	4·5
209	5,200,000	5·0
199 (with slight infection)	4,900,000	8·0

Neoplasms: benign tumours, if uncomplicated, do not affect the S. R. as a rule, whereas malignant tumours almost always accelerate the S. R.

The question, therefore, arises ' can the S. T. afford help in the differentiation of malignancy from conditions simulating it? ' In the series of cases collected personally it would seem that an acceleration of the S. R. occurs in all cases of malignant disease, except in that type which arises in epithelium, such as epithelioma of the tongue or penis; and cancer of the uterine cervix may show a normal S. R. However, as these cases from their superficial position present little difficulty in clinical diagnosis, the S. T. would serve no useful purpose. It is in such cases as carcinoma of the stomach or other internal organs, where present methods of investigation cannot penetrate with assurance, that the S. T. can be of help in giving a further opinion which may turn the balance of evidence for or against malignancy. This question will be more fully dealt with in the next section.

(c) *The Application of the S. T. to Clinical Medicine*

(i) *General infections.* As a rule all acute febrile disturbances are accompanied by an augmentation of the S. R., but there is no parallelism between the temperature elevation and the S. R. curve. Moreover, there is no relation between the degree of leucocytosis and the rapidity of sedimentation.

As both temperature and leucocyte count return to a normal figure long before the S. R., we realize that the S. T. is a far more delicate index of the effect produced upon the organism by the infecting agent. Moreover, when recovery from illness is complete, a swing of the pendulum takes place in the other direction; the S. R. during late convalescence becomes even slower than normal for a time, showing that when the infective process is at an end the organism, which has put forth all efforts to restabilize the equilibrium of the blood, continues for a time to produce this effect until an excessively high degree of stability is attained, as evidenced by decreased S. R. This finding has been confirmed by Rossier (36), who demonstrated similar changes in the curve of the iso-electric points which ran parallel with the S. R.

On the other hand, such is the delicacy of the sedimentation reaction that the occurrence of complications during convalescence from any febrile disease may be detected at an earlier stage by means of the S. T. than by clinical manifestations. If, for example, a case of scarlet fever is being kept under observation by repeated sedimentation tests, the S. R. will be found to diminish progressively when the effects of the toxic process are waning, but with the onset of any complications such as nephritis, otitis media, &c.,

we find a sudden increase in the S. R., which is succeeded in a few days by the clinical manifestations.

The fluctuations of the S. R. are well seen during the course of chronic inflammatory conditions such as pulmonary tuberculosis, in which sphere the value of the S. T. has gained almost universal acknowledgement.

Case 318 is an example of the return to normal of the S. R. in a boy who was admitted to hospital with non-resolution of a pneumonic process. He was suspected of having a tuberculous lung, but the innocent nature of his condition was proved, and after a month's stay in hospital he was discharged in a very healthy condition. He was febrile on admission and his attack of pneumonia dated from three weeks previously.

Date.	Red cell count.	S.R.
23.8.29	5,050,000	15·0 mm.
10.9.29	4,860,000	6·0 mm.
24.9.29	4,800,000	3·0 mm.

In spite of the fact that his temperature fell on the third day after admission the S. R. made a very slow return to normal.

A severe coryza, tonsillitis, bronchitis, and similar acute infectious processes accelerate the S. R. but slightly as a rule; only graver cases cause a marked increase when the toxic absorption and systemic disturbance are greater.

Acute rheumatic infections, typhoid fever, nephritis, and ulcerative endocarditis decrease the suspension stability.

Newham (37) investigated the S. R. in various tropical diseases, and reports an increased rapidity in certain types of nodular leprosy, especially where ulceration of the nodules has occurred, but in the anaesthetic variety of leprosy there is no increase in the rapidity of sedimentation. Kala-azar, sprue, liver abscess, and malaria are all accompanied by an augmented S. R.

(ii) *Diseases of the alimentary system.* In an examination for disease of the alimentary system no type of investigation can outweigh the value of a methodical and carefully taken history. It may be, however, that at the end of an exhaustive clinical and radiographical search we are still unable to reach a definite decision as to the diagnosis. It is in such cases that the S.T. may be of help. Thus simple ulceration may be distinguished from malignant conditions, and functional spasm from carcinomatous strictures.

Carcinoma of the oesophagus gives an acceleration of S. R., but seems to be accompanied by a polycythaemia, possibly on account of the dehydration present in these cases due to inability to take sufficient nourishment.

Example: Case 16, a man, aged 44 years, very cachectic, who had suffered from a growth of the oesophagus for 12 months.

Red cell count.	S.R.	Colour index.	Volume index.
5,500,000	15·0	0·76	0·86

When it is considered that this blood count is made on a specimen of blood which is diluted by 10 per cent. of its volume of citrate solution, then the normal undiluted blood would contain 6,000,000 red cells per c.mm. The

toxic effect upon the haemopoietic system is well seen in the small size of the cells and the low haemoglobin content. This concentration of the blood in oesophageal carcinoma had been confirmed by Gram (*loc. cit.*), Rubin (38), and Master (39), so that, in a case where the S. R. is doubtful, the value of correction for the red cell concentration is evident.

With regard to the differential diagnosis of carcinoma ventriculi from ulcus ventriculi there is a discordance amongst the various authors who have utilized the S. T. in this direction. Gram (*loc. cit.*) finds a normal S. R. in the large majority of ulcers, whilst carcinomata show an accelerated rate. Rubin (*loc. cit.*), who studied the S. T. extensively, examined 500 cases in the Cancer Service of the Montefiore Hospital, New York. He does not think that the S. T. can differentiate between simple and malignant ulceration owing to the frequent occurrence of a rapid S. R. in the former. Kovács (40) affirms the value of the S. T. in the domain of gastro-intestinal diagnosis, whilst Hoffgaard (41) also recommends the S. T. in the differentiation between gastric ulcer and carcinoma.

My own observations indicate that gastric or duodenal ulceration is accompanied by a normal S. R., whereas a gastric carcinoma causes an acceleration of the S. R. It may happen that a rapid S. R. is noted for a time in a case of gastric ulcer; such a finding would lead one to suspect a certain degree of toxic absorption from the raw area.

Evidence based upon some accidental findings during the course of a series of experiments on rabbits induces me to presume that an ulceration of the mucous membrane is in no small part due to bacterial infarctions of fine capillaries in the stomach wall. Such a septic process would naturally lead to a rapid S. R. The incident referred to occurred during an induction of an artificial septicaemia in rabbit No. 19. The rabbit was subjected to an intravenous injection of an emulsion of a haemolytic *Staphylococcus albus* isolated from the blood of a patient suffering from septicaemia. In this patient an organism precisely identical was cultured from an apical dental abscess. Two days later when, at the conclusion of the experiment, the animal was killed, an autopsy revealed, in addition to generalized septicaemic abscesses, three dark rounded areas accurately circumscribed on the anterior surface of the stomach just at the point of inosculation of capillaries coming from the anterior and posterior groups of arteries. They were found to be areas of haemorrhagic necrosis involving all the layers within the peritoneal covering, and the mucous membrane lining of the stomach corresponding to these foci was observed to be totally denuded, resulting in the formation of three ragged ulcers. Such a production of true acute gastric ulceration by the intravenous introduction of haemolytic organisms obtained indirectly from an apical dental abscess is a significant point, lending further support to somewhat similar work by other authors. Moreover, such an origin would account for the rapid S. R. and the fever often found to coexist with some gastric ulcers which are merely regarded as expressions of the reaction to an infective process.

When, therefore, the ulcer heals, a return to normal of the S. R. will be found, whereas, on the contrary, repeated estimations of the S. R. in malignant cases will continue to show an accelerated S. R.

Carcinoma of the stomach may give rise to a syndrome closely simulating that of pernicious anaemia, but even in spite of the occurrence of the same blood changes in both cases, when correction for the anaemia is made, the S. R. will usually remain high in gastric carcinomata, but it is always extremely slow in pernicious anaemia.

Gastric ulcer: Case 114. Non-complicated gastric ulcer of twelve months' duration.

Red cell count.	S.R.	Colour index.	Volume index.
4,970,000	1·0	0·99	1·01

Case 263. A Chinaman with a two years' history of duodenal ulcer. X-rays gave a positive finding. Red cell count, 4,770,000; S. R. 3·5. Re-done at a later date. Red cell count, 5,120,000; S. R. 3·5. The effect of treatment upon his blood count is seen, but the corrected S. R. remains unaltered.

Case 264 had a duodenal ulcer and was admitted on account of a severe haematemesis and melaena which reduced his blood count to 1,060,000 red cells per c.mm. He displayed a febrile reaction for more than a week later —possibly due to resorption of broken-down blood. Three weeks after admission a S. T. was performed. Red cell count, 3,470,000; S. R. 8·0. A rapid S. R. is remarked in this case and may be due to absorption from the site of the ulcer, or from the continued slight absorption of broken-down blood products.

It is to be noted that to eliminate the anaemic factor in such cases where the blood loss in itself causes a relatively rapid S. R., it is essential to correct for the red cell count.

Case 241, a man with a gastric ulcer, in whom the following evidence of septic absorption could readily account for the rapid S. R. present in his case. He had considerable pyorrhoea alveolaris, a leucocytosis of 14,600, and a daily rise of temperature. Red cell count, 5,160,000; S. R. 16·0. When, three days later, another specimen of blood was taken, the S. R. was already commencing to show a diminution. Red cell count, 5,480,000; S. R. 13·5. This drop in the S. R. is significant and helps to distinguish simple from malignant ulceration.

Gastric Carcinomata

Case No.	Remarks.	Red cell count.	S.R.
133	Jaundice present: X-ray diagnosis positive	3,480,000	12·5
99	X-ray diagnosis positive	5,060,000	16·5
126	Oesophagus also implicated	5,380,000	13·5
127	X-ray diagnosis positive. Large palpable lump	2,750,000	16·0
222	X-rays show stenosing pyloric growth	3,870,000	9·0
228	X-rays positive: palpable tumour	6,670,000	11·5
237	Blood picture typical of pernicious anaemia	1,610,000	2·75
242	X-rays show a large growth: pernicious anaemia syndrome present	2,820,000	14·5
253	Only two months' history: good state of nutrition	4,820,000	9·5
254	Complete pernicious anaemia syndrome	4,000,000	17·0
256	Two years' history: growth scirrhous in type	4,610,000	6·5

From the above table it is seen that a slow-growing tumour of scirrhous type does not accelerate the S. R. to the extent of large and more rapidly-growing tumours, some of which only gave a four to six weeks' history of symptoms. In three cases the clinical syndrome present was that of pernicious anaemia, except for the history of loss of weight, and in Case 237 there was a haematemesis one week previous to admission. The third of these cases had an enlarged spleen, whilst both the second and the third even had a superficial glossitis similar to that found in Addisonian anaemia. The blood film in each case, but more markedly in Case 237, showed poikilocytosis, anisocytosis, megaloblasts, and normocytes. Case 242, in addition to the rapid S. R., showed a leucocytosis of 36,500 which, of course, speaks against a diagnosis of pernicious anaemia.

That Case 237 should give such a slow S. R. I can only explain by the extreme distortion of the cells, which prevented rouleaux and agglutinate formation, which are indispensable factors in the production of a rapid S. R.

The S. T. is especially valuable in distinguishing the dyspepsia due to hyper- or hypo-acidity from that due to a cancer of the stomach and, when such a dyspepsia occurs in a nervous type of individual suffering from cancerophobia, the demonstration of a normal S. R. will help to bring back tranquillity to an overwrought mind.

Enteritis and colitis of an infectious origin give rise to an accelerated S. R., whereas simple diarrhoea will not alter the S. R. It must, of course, be borne in mind that the tendency of diarrhoea to cause dehydration, and thereby concentration of the blood, obviously necessitates a correction of the red cell count before proceeding to a S. T.

Case 176 is a patient who, during her stay in hospital, contracted bacillary dysentery when eight patients were implicated in the course of an epidemic outbreak. The S. R. for this particular individual had been done just previously, the figure obtained being as follows: Red cell count, 3,280,000; S. R. 3·0. During the attack of dysentery, red cell count, 4,770,000; S. R. 11·5. The concentrating effect upon the blood by the diarrhoea is well shown by the marked increase in the red cell count.

It is hardly necessary to reiterate the difficulty encountered in the differential diagnosis of disease in the lower part of the alimentary tract. We are always suspicious of carcinoma when a patient gives a history of constipation, alternating maybe with diarrhoea, and in the surgical department a complaint of haemorrhoids is frequently recorded. If, in such cases, a normal S. R. is found, it is unlikely that a carcinomatous or tuberculous lesion is present.

Case 415. A man, aged 58, complained of symptoms strongly suggestive of carcinoma coli. Radiological examination could reveal no abnormality beyond a mild diverticulitis. Red cell count, 4,370,000; S. R. 1·0.

Case 135. A man, aged 51, was strongly suspected to have a carcinoma high up in the rectum; there was a mass of internal piles, but no further abnormality was discovered.

Red cell count.	S.R.	Colour index.	Volume index.
4,930,000	4·0	1·01	1·14

On the other hand, carcinomata are usually accompanied by a rapid S. R.:

Case No.	Diagnosis.	Red cell count.	S.R.	Colour index.	Volume index.
102	Carcinoma of rectum	6,110,000	13·5	0·86	0·91
103	Carcinoma of rectum	4,400,000	17·0	0·75	0·78
141	Carcinoma of peritoneum with ascites	4,370,000	13·0	0·88	1·05
101	Carcinoma of head of pancreas	2,725,000	11·5	1·34	1·22
110	Carcinoma of liver	3,500,000	14·5	1·18	1·05
124	Carcinoma of liver	4,485,000	12·0	0·98	1·06

It is necessary to comment upon several of these cases. Firstly, Case 102 was a youth of only 22 years whose general health was good and the symptoms and physical signs were in favour of diverticulitis. He had an unusually high red cell count, but a rapid S. R. When a laparotomy was performed the malignant nature of his condition stood revealed.

Note the low colour index and volume index in the first three cases, but when the liver is involved, as in the last three cases, a high colour index and volume index are found.

The following case, No. 138, a child of 5 years, was admitted to hospital complaining of weight loss, slight cough, abdominal pain of a colicky nature, and constipation succeeded by mild diarrhoea. He was suspected to have a mild plastic type of abdominal tuberculosis, but the progress and after-history disproved this. The diagnosis ultimately made was atonic colon with intestinal stasis. The child put on weight in hospital and the general health was markedly improved, so that as a result of the tonic therapy employed he was enjoying perfect health when seen three months later. Whilst in hospital he was subjected to two sedimentation tests, the second one being performed after a minimal dose of tuberculin had been injected according to the routine of the specific test which I have utilized.

		Red cell count.	S.R.
Case no. 138.	Before tuberculin	4,660,000	3·5
	30 hours after tuberculin	5,140,000	3·5

Case 181, a boy, 6 years of age, was admitted with a mild plastic type of tuberculous peritonitis. He did not present much constitutional disturbance, but the abdomen was full and rather resistant, whilst ill-defined thickenings could be palpated in the upper abdomen and in the peri-caecal region. There was severe constipation and frequent attacks of colicky pain. He gave a definitely positive Von Pirquet test. When seen later, the abdominal colic continued from time to time. The S. R. was only slightly accelerated in this case and was in accordance with the low type of virulence present in this affection.

Red cell count.	S.R.	Colour index.	Volume index.
4,860,000	6·5	0·77	1·02

Case 207, a boy aged 9 years, gave a two months' history of abdominal

trouble. He was thin and pale, was occasionally pyrexial, and the abdomen was always full, very rigidly held, and generalized tenderness was constantly present. There was no difficulty in arriving at a clinical diagnosis of tuberculous peritonitis. Red cell count, 4,470,000; S. R. 14·0.

Case 206, however, presented great difficulty in diagnosis, but the weight of clinical evidence pointed in favour of tuberculous peritonitis. He was only 8 months old, but had been fed on cow's milk since the third week of life. In spite of a fairly healthy general appearance, weekly fluctuation of the weight curve was noted. From time to time the temperature rose to 100° F., the abdomen was tense and tender, and he was generally constipated. A very rapid S. R. was obtained, and this confirmed the diagnosis.

Red cell count.	S.R.	Leucocyte count.
4,660,000	18·0	12,600 (definite lymphocyte increase)

One case, an adult, with the ascitic variety of tuberculous peritonitis, gave an accelerated S. R.: Red cell count, 4,140,000; S. R. 11·0.

Affections of the liver. We turn now to pathological lesions of the liver, only to encounter many problems. The liver is an organ which subserves many functions, several of which seem to have a bearing upon the suspension stability of the blood, and, in consequence, when this organ is involved in certain pathological processes, the interpretation of the S. T. is extremely difficult. Accordingly, at an early stage in the history of the S. T., unexpected results were obtained when hepatic pathology was explored. As more investigators appeared in the field, so the discordant results published from time to time gave rise to varying explanatory statements, most of which centred round the fibrogenetic function of the liver. It has been claimed that fibrinogen is almost exclusively formed in the liver, therefore the finding of a slow S. R. in liver disease has called for an explanation based upon deficient production of fibrinogen as the cause. In my own series no diminution of the blood fibrinogen content has been discovered.

During the study of a series of cases exhibiting varied pathological lesions of the liver, I had been struck by several paradoxical results. In certain cases a rapid S. R. would be obtained, whereas almost exactly similar cases would show a slow S. R. It was remarked, moreover, that the presence of jaundice seemed to have an inhibiting effect upon sedimentation in some but not in others. It was decided, therefore, to probe this matter more deeply and see if any light could be shed upon the problem by means of the addition of bile-salts to blood *in vivo* and *in vitro*. A series of animals was employed and varying degrees of cholaemia were induced. The results of these experiments were embodied in two publications which appeared in 1930 (42 and 43), and the deductions arising from these experiments as applied to and confirmed by clinical findings may be stated thus: when retention of bile-salts occurs in the blood-stream there are three phases, (I) the first phase, where the concentration of bile-salts is not increased sufficiently to effect a slowing down of the S. R., because the plasma proteins

are able to adsorb these salts; (II) a second phase, where the cholaemia surpasses the power of adsorption of the proteins, with the result that the excess of bile salts increases the suspension stability of the red cells, thereby diminishing the S. R. to such an extent that it is difficult to attach any value to the employment of this sero-diagnostic reaction in the presence of neoplasms and inflammatory conditions; (III) a third phase, where the reactionary power of the organism is elevated and the effect of the bile-salts becomes nullified. The S. R. will again be influenced by the pathological process.

These findings help to explain the paradoxical results obtained, not only by myself, but by many other investigators.

The division of the cholaemic state into three phases readily explains the presence of a slow S. R. in early stages of an acute retentive jaundice, and the rapid S. R. found in long-standing cases.

Case Reports

Case No.	Clinical notes.	Red cell count.	S.R.
110	Gall stones: and mild jaundice	4,980,000	7·5
258	Gall stones: 8th day of deep jaundice	5,280,000	17·0
260	Gall stones: deep jaundice of 15 days' duration: markedly febrile	5,100,000	16·0
268	Stone in common duct: 3 months' jaundice and weight loss	4,970,000	14·0

Further illustrative cases are the following: Case 139, a girl of eleven years with hepatic and splenic cirrhosis, subject to periodic exacerbations of biliary retention, was examined on two occasions by means of the S. T. On the first occasion there was little icterus and there was no retention of bile-salts. On the second occasion, however, the S. T. was performed when the patient had a sudden exacerbation of jaundice, which was accompanied by a rigor and high pyrexia for several days. Bile-salts and pigments were found in the urine in large quantity on this second occasion. On each occasion a normal S. R. was found, although during the period of pyrexia an accelerated S. R. was expected. Evidently the acute retention of bile-salts was able to restabilize the colloid stability of the blood, for the surface tension-lowering substances can act as protectors of the red cells by surrounding them with a sort of supplementary membranous wall of surface-active molecules.

Results

	Red cell count.	S.R.	Colour index.	Volume index.	Fibrinogen.
Case no. 139	3,410,000	4·5	1·03	1·21	220 mg. %
Re-done during febrile state	3,570,000	4·5	1·05	1·23	230 mg. %

The increased size and haemoglobin content of the cells are noteworthy, whilst the fibrinogen is normal and varies little in the two specimens.

A comparison was made between two cases of toxaemia of pregnancy, in whom similar grades of toxaemia existed except for the presence of retentive jaundice in the second case. The first one showed a S. R. of 16·0 mm.,

whilst in the jaundiced woman a S. R. of only 7.0 mm. was observed. The fibrinogen content in both cases was more than double the normal figure.

No cases of sudden obstructive jaundice due to carcinoma or calculus were available, the only cases collected having been jaundiced for some little time. It is submitted, however, that when an obstructive jaundice develops, as a result of neoplastic pressure on the biliary system, the finding of a slow S. R. should not cause surprise or denial of the value of the S. R. in detecting the presence of carcinoma. When the early phase has passed, concurrently with the exaltation of the power of adsorption of the blood proteins for bile-salts, an accelerated S. R. will again be found.

When pathological lesions of the liver are present, great care is needed in interpreting the S. T., because this organ is closely bound up with the colloidal stability of the blood. When the proteopexic function is disturbed, heterogeneous proteins, absorbed from the alimentary tract, escape the damaged hepatic cellules and, gaining entrance into the blood-stream, upset the suspension stability of the plasma and an increased rapidity of sedimentation of the erythrocytes occurs. A combination of animal experimentation and human biological observation has led to the evolution of the haemoclasic sedimentation reaction, which is able to display the degree of disturbance of colloidal stability amongst certain elements of the blood-stream, during the digestion of a protein-containing meal. This work is, as yet, unpublished, but it suffices at the present instance to state that, to obviate fallacious readings of the S. R. in cases with hepatic pathology, the S. T. must be performed with the patient fasting. An understanding of this haemoclasic reaction enables one to explain the apparently controversial results obtained by many authors who utilized the S. T. during a routine examination of cases presenting hepatic pathological lesions.

The following is a brief report of the results obtained by authors in a variety of diseases of the liver and in cases of gall-stones.

Kovács (*loc. cit.*) finds a slower S. R. in diseases of the liver and in cases of gall-stones.

Plass and Rourke (44), after producing liver necrosis in dogs, record a reduced rate of sedimentation and a reduced fibrinogen content of the plasma.

Abderhalden (45) pointed out in 1921 that in jaundice the S. R. is decreased.

Gram (*loc. cit.*) included four cases of acute hepatitis in his series of investigations and reported a normal S. R. figure in two and a rapid S. R. in the other two; one case with cirrhosis of the liver gave a rapid S. R., and cases with cholelithiasis were found to give a rapid S. R. as a rule.

Newham (*loc. cit.*), during an investigation of certain types of tropical disease, came to the conclusion that an increased S. R. is to be expected where there is some definite derangement of the liver.

Kreindler and Popper (46), in 1924, described a few cases in which they found an accelerated S. R., three-quarters of an hour after the ingestion of milk, where some degree of acute parenchymatous hepatitis existed, such as catarrhal jaundice and acute atrophy of the liver.

A retarded S. R. was found in cases with hepatic cirrhosis, chronic venous congestion of the liver, secondary neoplastic conditions of the liver, and syphilitic icterus, whilst an unaltered S. R. was obtained in gall-stones and cured syphilitic icterus. The following table represents a number of cases with pathological lesions of the liver and two cases of acholuric jaundice investigated personally (surgical conditions of the hepatic system are excluded because they have already been quoted). Upon the large majority of these cases a haemoclasic crisis test was also performed.

Case No.	Diagnosis.	Clinical notes.	Red cell count.	S.R.
95	Acholuric jaundice	Acute exacerbation almost at an end	3,600,000	0·0
136	Acholuric jaundice	Bile-salts in urine (trace)	3,400,000	3·5
193	Congenital obliteration of bile-ducts	Urine contained bile-salts and pigments	3,420,000	9·5
90	Alcoholic hepatic and splenic cirrhosis	Retention of bile-pigments and salts	4,240,000	15·0
139	Primary hepatic and splenic cirrhosis	8 months' history of variable retentive jaundice	3,410,000	4·5
153	Case no. 139 re-done	Now in acute phase of retentive jaundice with rigors and pyrexia	3,570,000	4·5
279	Banti's disease: cirrhotic liver and spleen	Bile-salts + + in urine	3,950,000	14·0
200	Chronic hepatic and splenic cirrhosis of 'primary' type	Boy of 11 years: ascites: marked retention of bile-salts and pigments	3,180,000	4·5
238	Alcoholic hepatic cirrhosis	A 5 years' history: marked ascites: large output of bile-salts and pigments in urine	3,770,000	13·0
239	Alcoholic hepatic cirrhosis	Duration of illness 1 month: slight trace of bile-salts in urine	3,380,000	5·0
240	Alcoholic hepatic and splenic cirrhosis	A year's history: merely a trace of bile-salts and pigments in urine	3,020,000	15·5
246	Acute catarrhal jaundice superimposed upon alcoholic cirrhosis of liver	Symptoms for 15 days only: bile-salts and pigments in urine	4,190,000	1·5
	Case no. 246 repeated 5 days later	Still has retention of bile-products	4,070,000	1·5
	Case no. 246 re-done almost 4 months later	General health good; liver still enlarged. No bile-salt or pigment excretion in urine	4,180,000	2·5
257	Catarrhal jaundice. Acute phase now passing	No retention of bile-salts: pigments + in urine	4,920,000	10·5
259	Catarrhal jaundice. Acute phase passed	No bile-salt retention: chronic salpingitis also present	4,000,000	15·0
267	Catarrhal jaundice	1 week's history: still in acute phase with marked retention of bile-salts and pigments	6,820,000	8·0
413	Catarrhal jaundice. Acute phase passed	Approximately 10 days' history: slight bile-salt retention	3,550,000	3·0
121	Toxic hepatitis due to N.A.B. injections	Marked jaundice	3,910,000	5·0

The first point worthy of emphasis is the fact that, in practically all of these cases where a normal S. R. was found, some degree of anaemia was likewise present, and if correction for the diminished quantity of red cells had not been made a rapid S. R. figure would have been obtained. Here,

then, we have one explanation for the rapid rates of sedimentation found by many observers in hepatic disease.

The second point arises as a result of the investigation of a number of these cases by means of the haemoclasic crisis test. As already mentioned, definite damage of the hepatic parenchyma leads to an accelerated S. R. within the three hours which immediately follow the ingestion of a protein meal, or even a glass of milk. Therefore, a different S. R. will be obtained according to the time that the blood specimen is removed from the patient in relation to that patient's intake of food.

On analysing the above tabulated results we attain the following conclusions:

(1) Acholuric jaundice, which is a disease with no apparent influence upon hepatic metabolism, except in so far as a notable excretion of bile-salts occurred in the second case, exerts an accelerating influence upon the S. R.

(2) Congenital obliteration of the bile-ducts with at least eight weeks' history of retentive jaundice; this produces an accelerated S. R.

(3) Two children presenting a hepatic and splenic cirrhosis of unknown origin showed a normal S. R. In the one case the S. T. was repeated during an acute attack of jaundice with rigors and pyrexia and, although marked pyrexia is usually accompanied by an increased S. R., no increase took place on this occasion—possibly due to the protective influence of the excess of surface-active substances in the blood.

On the other hand, a true case of Banti's disease with a long history gave a rapid S. R. The retention of bile-salts noted in this patient was also probably of long standing, and may have produced such a reaction on the plasma proteins as not only to nullify the stabilizing influence of the bile-salts, but even to carry the reaction a step farther and produce, thereby, a decreased suspension stability.

(4) Alcoholic hepatic cirrhosis, when only of brief duration, as regards symptoms, is accompanied by no alteration in the S. R., but cases with a more severe grade of lesion, where the symptoms have been remarked for several months or years, seem to show a definitely accelerated S. R.

(5) One case of toxic hepatitis, following N. A. B. therapy, was found to have a normal S. R.

(6) Several cases of acute catarrhal jaundice were investigated and varying results were obtained. In the first place we note that the erythrocyte count does not show the reduction which almost constantly accompanied chronic hepatic cirrhosis. In two cases a rapid S. R. was found where a definite infective agent could be said to have precipitated the hepatitis. In one of these cases a frank attack of influenza had preceded the onset of jaundice, and in the other case a chronic pelvic inflammation was present. There was, incidentally, no bile-salt retention in either of these cases at the time the S. T. was done.

One of the cases of acute catarrhal jaundice—Case 267—had been receiving bismuth injections for the treatment of syphilis, so that the slight

acceleration of S. R. in his case might have been due to the specific infection. Certainly he still had a very slight augmented S. R. when another test was performed three weeks later.

The other cases showed a normal slow S. R.

(7) An increase in size of erythrocytes was found in a few cases investigated, but the colour index was almost normal. These findings fall in line with previously noted high volume index figures noted in diseases of the liver.

Case No.	Diagnosis.	Colour index.	Volume index.
193	Congenital obliteration of bile-ducts	0·95	1·33
90	Alcoholic hepatic and splenic cirrhosis	0·96	1·00
139	Primary hepatic and splenic cirrhosis	1·03	1·21
153	Same case later during acute retentive phase	1·05	1·23
200	Chronic hepatic and splenic cirrhosis of 'primary' type	1·25	1·21
121	Toxic hepatitis	1·02	1.19

(iii) *Diseases of the blood and cardiovascular system.* A simple anaemia, as already pointed out, appears to cause a rapid S. R., but correction of the blood count will slow down the S. R., which will then give a result according to the primary condition responsible for the anaemia.

If the anaemia is due to haemorrhage, for example, then correction of the erythrocyte count changes the rapid S. R. figure to a normal one. If the anaemia is secondary to malignant or some infective process, then correction for the anaemia will slow down the S.R. to some extent, but the final corrected figure will still be higher than normal, and will faithfully mirror the effect produced upon the organism by the pathological process.

The majority of authors state that in pernicious anaemia an accelerated S. R. is found. They do not, however, make any allowance for the extremely low blood count found. I have investigated two cases, and the following were the figures obtained:

Case No.	Red cell count.	Uncorrected S.R.	Corrected S.R.	Colour index.	Volume index.
130	1,260,000	27·5 mm.	0·0	1·35	1·34
227	2,800,000	13·5 mm.	0·0	—	1·40

The S. R. was also measured in tubes containing four million red cells per c.mm., and in the first case no fall was observed, whilst in the second case merely 6·5 mm. fall was noted. From these two cases it would appear that the corrected S. R. in pernicious anaemia is very much slower than normal, and the explanation submitted for this delayed fall is that deficient rouleaux and agglutinate formations occur, due to the unevenness of the shape and size of the cells.

In virtue of the red cell concentration polycythaemia causes a diminished S. R., unless the red cell count is corrected. The following observations were recorded:

Case No.	Clinical notes.	Red cell count.	Uncorrected S.R.	Corrected S.R.
244	A woman, aged 41 years	7,640,000	0	6·0
245	A man, aged 54 years: the slightly rapid S.R. is due to tissue breakdown associated with X-ray treatment	8,700,000	0	7·5
248	A man, aged 55 years, who had already responded well to treatment, but had received no X-ray therapy for 9 months	5,120,000	3·5	4·0
249	A man, aged 55 years, still receiving treatment	5,900,000	5·0	8·5

Acholuric jaundice, as already shown, is associated with an extremely slow S. R. It is a noteworthy feature of haemolytic processes that a very slow S. R. is found, for we also see a very retarded S. R. in pernicious anaemia and in new-born infants where, even in the absence of obvious icterus, the deep yellow colour of their plasma indicates the latent haemolytic activity.

Diseases of the heart and vessels: During recent years the S. T. has gained ground as a prognostic agent in cases of rheumatic fever. It is found to be a more reliable index of activity than the temperature, leucocyte count, or even the pulse-rate, and when massive salicylate therapy is being exhibited, thus masking important symptoms and physical signs, the employment of the S. T. will be an added check on the course of the disease.

I have little experience of the use of the S. T. in this connexion, but there is no doubt that acute rheumatic infections cause a rapid S. R. which diminishes and reattains the normal level when activity of the process is at an end.

Case 262, a girl, aged 16 years, who had had a frank attack of rheumatic fever two months previously, with affection of the myocardium, still showed evidence of slight activity of the rheumatic process by the intermittent peaks of temperature and the persistent tachycardia when the S. T. was performed. The S. R. was accelerated, but only moderately so:

Red cell count.	S.R.	Leucocyte count.
5,020,000	9·5	9,200

Case 530 was thought to be free of activity five weeks after admission, as he was afebrile, the tachycardia had subsided, and the leucocyte count had fallen to 8,000 per c.mm. Before allowing him to get up a S. T. was performed and revealed the following results: red cell count, 4,270,000; S. R. 17·0. Three weeks later he was still afebrile and, although the pulse was occasionally unsteady, the rate usually lay between 70 and 90. He was allowed out of bed for a short while, but latent activity was demonstrated by a slight rise in temperature and pulse-rate. Another S. T. was performed: red cell count, 4,090,000; S. R. 17·0 mm.

Case 531 was improving steadily six weeks after admission and had been afebrile for some time. Red cell count, 4,790,000; S. R. 8·0 mm. Three weeks later the S. R. was re-done. Red cell count, 4,710,000; S. R. 5·0 mm. In this case a steady improvement in his condition was revealed by the S. T., whereas in Case 530 latent activity was easily demonstrated by the persistently high S. R.

A case of cardiac failure with auricular fibrillation and pyrexia had a rapid S. R. which later slowed up coincidentally with improvement of the condition and with the appearance of a normal cardiac rhythm.

Frosch (47) quotes cases of infective endocarditis where high S. R. figures were obtained with subsequent progressive increase until death.

Arteriosclerosis and hyperpiesis, with no underlying infection, give a normal S. R.

Case 223, a man, aged 62, was admitted with a recent hemiplegia due to cerebral thrombosis incidental to arteriosclerotic changes. The Wassermann reaction was negative. There was an occasional rise of temperature during the first few days after admission, so when the temperature had completely subsided a S. T. was performed. Red cell count, 4,000,000; S. R. 2·5.

Raynaud's disease: Two cases were investigated and a rapid S. R. was found in each case on correction for the increased erythrocyte content. The cause of this rapid S. R. is not apparent.

Case No.		Red cell count.	S.R.
231	A woman aged 43 years	5,740,000	10·5
233	A girl aged 17 years	5,220,000	7·0

(iv) *Diseases of the respiratory system*: In the field of pulmonary tuberculosis the S. R. has proved itself of immense value. Probably in no other branch of medicine has the test enjoyed such extensive use, especially by workers on the Continent and in America. I have records of more than 166 tests made upon 71 tuberculous individuals, some of whom were repeatedly investigated over a period of four months during their stay in a sanatorium. The S. T. represents the intensity and degree of activity of the process; moreover a normal S. R. has never been found with an active tuberculous focus. The S. R proves a most truthful guide, comparing more closely with the radiological evidence than with other diagnostic procedures, and, when the radiographic findings are equivocal, the S. T. can detect improvement or retrogression before any other methods.

Acute infections of the respiratory tract cause augmentation of the S. R., and a return to normal of the S. R. takes place at a much later date than subsidence of the febrile reaction.

Pneumonia markedly accelerates the S. R., which returns to normal several weeks after the crisis.

Acute bronchitis is accompanied by a rapid S. R. which slowly returns to normal, but chronic bronchitis usually gives rise to a slight elevation of the S. R., although, if the constitutional disturbance is very slight, a normal S. R. may obtain.

Asthma may give a normal or slightly accelerated S. R., but certain allergic phenomena intervene which influence the S. R. according to the state of the colloidal equilibrium of the blood at the moment when the test is performed.

Tuberculous pleural effusion always occasions an acccleration of the S. R.

Tabulated Results

Case No.	Diagnosis.	Red cell count.	S.R.
174	A child with broncho-pneumonia and meningism	4,050,000	13·0
318	Delayed resolution of lobar pneumonia, still pyrexial 3 weeks after onset	5,050,000	15·0
	Case no. 318, re-done 3 weeks later	4,860,000	6·0
	Case no. 318, re-done after a further 3 weeks, now healthy and well	4,800,000	3·0
261	Convalescent from influenza: afebrile now for 3 days	4,200,000	12·0
214	Pleural effusion of 4 months' duration	4,630,000	15·0
220	Pleural effusion of 2 weeks' duration	5,580,000	15·0
225	Asthma and chronic bronchitis, pyrexial	4,060,000	8·5
269	Chronic bronchitis and emphysema	4,870,000	10·5
215	Asthma, of allergic type	5,520,000	2·5
250	Cyclical asthma and eczema: asthma one month ago: eczema now present	5,430,000	8·0
299	Chronic non-specific bronchitis: Wassermann reaction positive	5,040,000	8·5

The slow return to normal of the S. R. is well seen in Case 318. He gained weight and strength whilst in hospital, slowly at first, more rapidly later, and the temperature fell about three days after admission. The more delicate S. T. signalized that the suspension stability of the blood took much longer to attain a normal equilibrium.

(v) *Diseases of the central nervous system.* Little personal work has been done in this direction, but of late years neurologists and psychiatrists have widened the scope of the S. T. by its extensive employment in the differential diagnosis of diseases of the central nervous system. The majority of authors agree that a normal S. R. obtains in functional nervous disorders.

Glaus (48), who applied the test in cases of psychoses, found an increased S. R. in senile dementia, neurosyphilis, general paralysis of the insane, katatonia, and immediately after epileptic seizures, but he found no increase in neurasthenia, hysteria, paranoia, or manic-depressive psychoses.

Pijper and Russell (*loc. cit.*) employed the S. T. in 625 cases of mental disease, and found an increasing incidence of a rapid S. R. with progression of the disease in dementia praecox. A positive Wassermann reaction was accompanied by a rapid S. R. and untreated cases of G. P. I. gave an increased S. R., whilst treatment of such cases by vigorous methods led to a decrease in the S. R.

Alcoholic psychosis gave a rapid S. R. in 75 per cent. of cases, but this condition, of course, is related to the series of alcoholic hepatic cirrhosis already described, and long-standing hepatic cirrhosis gives rise to a rapid S. R.

Coeytaux (*loc. cit.*) finds that organic disease of the central nervous system, where the origin is non-infectious, gives a normal S. R.; such cases are hemiplegia, sciatica, and cerebral softenings. Polyneuritis gives rise to a slight acceleration of S. R., but Parkinson's disease and encephalitis lethargica give contradictory results.

Personal Observations

Case No.	Clinical notes.	Red cell count.	S.R.
100	Sciatica. (The normal S.R. figure rules out nerve-root pains due to neoplastic formation.)	4,900,000	3·0
122	Disseminated sclerosis	4,960,000	3·0
223	Hysterical paralysis of right arm and left leg with 'glove and stocking' anaesthesia. There was a mild pyrexia from time to time	5,030,000	7·0
212	Post-encephalitic Parkinsonism—pyrexial	5,900,000	7·5

Cerebral tumours cause a rapid S. R. if they are malignant, but if their duration is long the S. R. is not greatly accelerated. The following results were obtained:

Case No.	Diagnosis.	Red cell count.	S.R.	Colour index.	Volume index.
208	Cerebellar neoplasm with a two years' history	4,990,000	3·0	0·85	1·10
98	Meningioma found at operation	5,440,000	6·5	0·91	1·0
251	Acromegaly due to adenoma of pituitary	4,760,000	16·5	—	—
189	Infiltrating pontine glioma	4,970,000	8·5	1·00	1·10

The first of these cases presented the clinical picture of a very slow-growing cerebellar neoplasm whose nature was rather benign. A normal S. R. indicated the absence of constitutional upset in this case.

The second patient gave a S. R. reading which is on the border line and as such is of little help in diagnosis.

In the third instance, a very rapid S. R. was noted during the investigation of a patient with acromegaly where radiological evidence clearly demonstrated an erosion of the sella turcica due to an adenomatous growth. One would have expected to find a slow S. R. with this benign type of tumour, and perhaps the tumour itself was not responsible for the rapid S. R.

The fourth case was a child who, at operation, was found to have a large glioma infiltrating the pons; the malignant nature of the growth was apparent from the relatively short history and microscopical examination, whilst the S. R. figure was in accordance with the clinical picture.

Various disorders and intoxications. Several cases of diabetes were investigated. In the majority of these cases a very low plasma specific gravity was found, and the S. R. appeared to be uninfluenced by the hyperglycaemia.

Case No.	Diagnosis.	Blood sugar mg. %	Red cell count.	S.R.	Specific gravity of plasma.
33	Dry diabetic gangrene.	180	3,540,000	3·5	1020·5
37	Hyperglycaemia and anasarca	157	5,420,000	13·5	1021·9
42	Diabetes	220	4,970,000	7·5	1024·5
117	Diabetes	200	5,490,000	3·5	1030·0

One patient with nephritis was examined to see if an elevation of the urea content of the blood influenced the S. R. in any way. Cabanis (49) reports seven cases of uraemia, in each of whom an accelerated S. R. was found. It is hardly likely that such an inert substance as urea should influence the colloidal stability, and in his seven cases the acceleration of

S. R. was probably due to the metabolic derangement and alteration of the plasma proteins rather than to an elevated urea content.

Case 65 is a girl of 25 years with uraemia and hydraemia, and, had not correction been made for the low red cell content, a very rapid S. R. would have been obtained.

Red cell count.	S.R.	Blood urea.	Specific gravity of plasma.
2,470,000	6·5	135 mg. %	1026·3

Several cases of nephritis in children came under observation, two of them being submitted to repeated sedimentation tests during the course of their stay in hospital, and in this way some interesting data were obtained with regard to the S. R. in relation to alterations in amount of the plasma proteins.

Case No.	Clinical notes.	Red cell count.	S.R.	Cholesterol.	Plasma proteins.		
					F.	A.	G.
115	Subacute nephritis	1,470,000	11·0	—	0·350	—	—
143	Acute nephritis due to tonsillitis: pyrexial	3,290,000	12·0	—	0·522	3·28	1·46
	No. 143 re-done a month after admission when marked improvement in her condition had taken place	3,280,000	3·0	—	0·341	3·18	2·02
158	Chronic parenchymatous nephritis of nephrosis type with marked oedema, lipaemia	3,200,000	11·0	397 mg. %	0·384	2·43	1·00
163	Acute attack of nephritis superimposed on a chronic parenchymatous lesion of nephrosis type: oedema and lipaemia + +	5,200,000	15·5	546 mg. %	0·727	3·60	0·642

Very little help is afforded the clinician by the employment of the S. T. in nephritis, because in both the acute and chronic stage a rapid rate of sedimentation is obtained. Case 143 was very interesting because on admission to hospital she was just suffering from her first attack of nephritis incidental to an acute tonsillitis. A rapid S. R. was found on this occasion, but when, a month later, all fever having subsided and the albuminuria having practically ceased, she was subjected to another S. T., a normal figure was obtained. At a later date tonsillectomy was performed and the renal lesion cleared up completely. But in this case, before the tonsillectomy, an attack of bacillary dysentery caused a set-back in convalescence, and a S. T. performed during this acute febrile disease showed an increase of S. R. from the normal figure of 3·0 mm. up to 11·5 mm.

Rheumatic conditions. The acute, febrile stage is accompanied by a rapid S. R., which diminishes with retrogression of the toxaemia.

As mentioned in the surgical section, acute joint conditions, such as gout, during the febrile attack, acute polyarticular rheumatism, acute polyarticular rheumatoid arthritis, and acute infective arthritis cause an acceleration of

the S. R. Chronic progressive polyarthritis, even in the absence of fever, usually augments the S. R.

The value of the S. T. does not lie in the diagnosis of these conditions, but rather in the evaluation of prognosis and in its ability, in such a condition as rheumatic fever, to indicate the presence or absence of latent infection. This, of course, means repetition of the test from time to time during the course of the illness, but in this way a more delicate standard is assured than is afforded by the temperature, leucocyte, or pulse curve.

Allergic diathesis. The amount of research and the ever-increasing publications upon this subject are sufficient evidence of the protean manifestations of this little-understood condition. It is inextricably bound up with the phenomena of colloidal stability, and it is upon these lines that a solution to the problem may ultimately be attained. In my investigations, I had the advantage of working with Dr. Joltrain, Director of the Research Laboratory of the Cochin Hospital in Paris, who has spent ten years in investigating the colloidoclasic diathesis. In collaboration with him, three papers (42, 43, 50) were published on the results of some experimental work upon various anaphylactic shock phenomena in animals.

A remarkable feature of allergic phenomena is the periodicity of attacks, and in some types of case a definite cycle is observable. One of the cases examined, for example, had for some time suffered from cyclical asthma and eczema, and when one complaint disappeared it was succeeded by the other. Similarly, another patient had for years suffered from recurrent eczema and psoriasis, chiefly during the winter and spring.

Widal was the first to demonstrate the train of haemovascular phenomena which coincided with the outwardly visible manifestations of the allergic diathesis, and he pointed out the similarity which exists between these phenomena and those described by Richet, who was the first to discover the state of anaphylaxis. The only difference between the two conditions is the abruptness of the change which occurs in anaphylactic shock as compared with the slow evolution of the changes occurring during the haemoclasic shock described by Widal.

The allergic diathesis was shown by Widal to be characterized by a certain series of modifications of the blood and blood-vessels when a protein-containing meal—even half-a-pint of milk—was ingested by a fasting patient.

The manifestations were proved to be dependent upon a deficiency in the proteopexic function of the liver, which allowed incompletely disintegrated proteins, absorbed from the alimentary tract, to pass through into the general circulation. He claimed that these modifications—such as diminution of the blood-pressure, surface tension, refractometric index, leucocyte count (with inversion of the differential formula), of the PH and alkaline reserve, along with increase of coagulability of the blood—were brought about by a change in the colloidal stability. None of these factors would seem to depend upon the colloidal stability, however, but the theory was correct, nevertheless, as I was able to prove by the employment of the S. T.

during the production of the haemoclasic shock. Each case investigated showed a certain series of modifications of the S. R. which were reproduced in animals when they were subjected to anaphylactoid shock by the intravenous injection of peptone solutions.

In normal individuals no variation in red cell count or S. R. occurred during the haemoclasic crisis test, but with definite hepatic lesions a rise in the red cell count was remarked in company with an acceleration of the S. R.

Only two allergic cases were subjected to the haemoclasic sedimentation reaction, but the findings were similar to those in the group of patients with a hepatic lesion, viz. an increase in the red cell count and marked acceleration of the S. R.

Consideration of the foregoing material enables us to understand why in some of the cases about to be quoted a rapid S. R. was found, whilst in others a perfectly normal figure was obtained. A rapid S. R. figure in some of these cases denoted that the blood was in a state of decreased suspension stability at the time when the test was performed. The clinical details quoted support this view.

Protocols

Case No.	Clinical notes.	Red cell count.	S.R.
40	Admitted for investigation: pyrexia of indeterminable origin: symptoms suggestive of neurasthenia: recurrent psoriasis and eczema each winter and spring	5,060,000	8·3
215	Asthma due to specific protein sensitization. No attacks for a few weeks	5,520,000	2·5
232	Asthma: specific sensitivity to insulin. No recent attacks	5,420,000	4·5
216	Migraine: attending the hospital for protein desensitization	4,900,000	6·0
250	Cyclical asthma and eczema: asthma ceased a month ago: eczema then commenced and is still present	5,430,000	8·0
382	Urticaria of alimentary origin: placed on a régime for 6 days with animal proteins excluded.	4,600,000	6·0
219	Quincke's oedema: attacks still occur: marked dermatographism present	4,560,000	13·5

The first patient was labelled clinically as neurasthenia. However, a rise in temperature appeared from time to time, and in the history it came to light that she had suffered in the past from psoriasis and eczema, which recurred each winter and spring. Moreover, there had been frequent attacks of tonsillitis and influenza, especially during the previous twelve months. This history and the slightly rapid S. R. would suggest the existence of some latent focus of infection, which was signalized by the intermittent mild pyrexia, and caused the cyclical skin lesions.

No comment need be passed upon the next case, but the third patient is extremely interesting from the point of view of the aetiology of his asthma. A full description is to be found in Joltrain's recently published book, *Les Urticaires* (Paris). This patient was strongly allergic to pure, crystalline insulin, with which Joltrain worked. At the time when the S. T. was performed he had been free of asthmatic attacks for some days, so it may be assumed that his blood had regained a normal equilibrium when the normal S. R. figure was obtained.

The fifth case on the list gave a slightly rapid S. R. indicating the presence of colloidal instability in a patient who was suffering from cyclical eczema and asthma.

The next case gives a S. R. which is just on the border line, but since admission to hospital, six days previously, he had been kept on a diet from which all animal proteins had been excluded because the complaint was thought to have its origin in an alimentary sensitization. When a haemoclasic crisis test was performed, the S. R. was increased from 6·0 mm. to 11·0 mm., so probably had the S. T. been performed when urticaria was still present, a week previously, a more rapid S. R. would have been found.

The last case would seem to support this statement. He was investigated whilst uticarial phenomena still persisted and marked dermatographism was demonstrable. A very rapid S. R. of 13·5 mm. connoted a distinct colloidal instability of the blood elements.

Syphilis. Active lesions cause a moderate acceleration of the S. R., whilst diminution in the rate runs parallel with a successful response to treatment.

It is not suggested that the S. T. be used as a diagnostic agent in this disease except in the new-born, but the fact that syphilis can cause some acceleration of the S. R. must be kept in mind when other diseases are being investigated. In the new-born, however, the S. T. may be of great value in detecting congenital syphilis.

György (*loc. cit.*) found that, if other causes could be excluded, a marked increase in sedimentation velocity in infants under 1 month of age could be considered as diagnostic of syphilis, as its occurrence was paralleled by a positive Wassermann reaction and Sachs-Georgi reaction: moreover, the S. R. diminished with successful antisyphilitic treatment.

Minamide (51) also regards the finding of a rapid S. R. in nursing infants as of great importance in the diagnosis of hereditary syphilis.

Pijper and Russell (*loc. cit.*) state that a rapid S. R. in an infant of under 1 month of age almost always means congenital lues, as there are hardly any other affections which can produce such a S. R. at that period. It is all the more valuable because the Wassermann reaction is so frequently negative at this stage, and symptoms such as coryza and rash appear much later.

These results are confirmed by Coeytaux (*loc. cit.*) who found an extremely rapid S. R. in children possessing at the same time a positive Wassermann reaction. He states emphatically that the finding of a very rapid S. R. in an afebrile child who presents no other sign beyond, perhaps, slight retardation in growth, should immediately direct the attention to the possibility of hereditary syphilis, even in the face of a negative Wassermann reaction. In his cases he found arsenical therapy brought about a definite retardation in the S. R.

Addison's disease. Only three cases of this description have been examined, but a rapid S. R. was found in two, and a retarded S. R. in one:

Case No.	Red cell count.	S.R.
417	4,210,000	10·5
532	5,270,000	11·0
533	3,810,000	0·0

Two Spanish authors, Bonilla and Moya (52), on the other hand, found that the S. R. was decreased in their series of twenty-four cases, and from this they conclude that the S. T. is the most reliable observation for the diagnosis of suprarenal impairment.

Paediatrics. Mention has already been made of the values obtained in normal children. Like the adult, the infant responds to all febrile infectious diseases by an acceleration of the S. R.; whatever the condition, otitis media, osteomyelitis, pneumonia, septicaemia, acute tonsillitis, scarlet fever, tuberculosis, nephritis, &c., all produce a rapid S. R. Gastro-enteritis of an infectious origin gives a markedly rapid S. R., whilst, if of alimentary origin, a normal figure is found—according to Wolf (53).

The S. T. proves of great value in the differential diagnosis and prognosis of tuberculous infections of children, just as in the case of adults.

Nephritis has already been discussed in the section on general medicine.

Pyelitis causes a moderate acceleration of the S. R., but nephrolithiasis is accompanied by a normal S. R.

Case No	Diagnosis.	Red cell count.	S.R.	Leucocytes.
146	Congenital morbus cordis with pyelitis	5,990,000	9·0	16,600
209	Renal calculus (afebrile)	5,200,000	5·0	—

Two cases of typhoid fever in children came under observation and several tests were performed upon them at different stages of the illness.

Protocols

Case No.	Clinical notes.	Red cell count.	S.R.	Colour index.	Volume index.
137	Typhoid fever during convalescence. Pulse-rate and temperature normal for 2 weeks	4,440,000	12·5	0·9	0·98
	Same case 18 days later: health improving	4,700,000	7·5	0·9	0·98
142	Case of chorea with typhoid infection superadded. Blood specimen taken at end of defervescent stage	4,260,000	11·5	0·75	1·00
	Same case: normal convalescence—10 days later	4,480,000	10·5	0·85	1·07
	19 days later: improving steadily	4,330,000	4·5	0·85	1·05
	Quite normal state of health—24 days later	4,090,000	0·5	1·0	1·18

The most important feature that calls for attention is the extreme length of time taken by the blood to regain its stability, which was so disorganized by the typhoid infection. In the first case a slightly accelerated S. R. was still present 32 days after the cessation of all pyrexia, and in the second case a normal S. R. figure was only attained 29 days after defervescence. A further decrease in the S. R. was found in another 24 days, showing that the colloidal stability of the blood swings in an opposite direction when an infective process is at an end. The slow but steady increase in the size of the red cells and in their haemoglobin content is a feature of the second case.

Case 211 was examined during the convalescent stage which succeeded a febrile attack of acute otitis media. The child was only 15 weeks old and

suffered from pylorospasm which had produced a certain amount of debility, thereby predisposing him to infective processes.

Red cell count.	S.R.	Leucocytes.
3,030,000	0·0	7,400

A markedly increased suspension stability is remarked in this case and indicates a complete subsidence of any inflammatory focus.

Case 202 is a baby of 4½ months, in whom an anomalous S. R. was obtained. Admitted with meningism and an extreme degree of irritability, this child was afebrile and presented a very good state of nutrition. Gradually the irritability lessened and, seven days after admission, health seemed perfectly normal when the S. T. was performed. The Von Pirquet reaction was negative. During the ensuing six days rapid downhill progress occurred, and three days before death pyrexia was noted for the first time. The post-mortem findings were characteristic of acute encephalitis.

Haematological examination during the quiescent period :

Red cell count.	S.R.	Leucocyte count.
4,150,000	4·0	17,500

Case 185, an early cretin, aged 1 year, gave the following figures :

Red cell count.	S.R.	Leucocyte count.
4,100,000	5·5	10,000

Rickets : Two cases were examined. *Case 197*, a child aged 2 years 5 months, with healing rickets, gave the following blood picture : Red cell count, 4,350,000 ; S. R. 3·25. But the second one, *Case 198*, a child aged 1 year 11 months, gave an accelerated S. R., due, no doubt, to marked catarrhal infection of the respiratory tract. In spite of a month's treatment in hospital, including ultra violet light therapy, the child gained ground but slowly, and there was a persistent nasopharyngitis associated with bronchitis. The child looked well, however, and the underlying toxic foci were only really portrayed by the following haematological examination :

Red cell count.	S.R.	Leucocyte count.
4,630,000	11·0	43,000

Summary

1. A new and simple technique for the performance of the sedimentation test is described, which avoids certain fallacies and places the test upon a standard basis, so that an exact comparison of the sedimentation rate in various samples of blood may be made.

2. The chief correction is that for an abnormal blood count. A method is given for bringing the citrated blood before measurement of the sedimentation rate to a standard content of 5,000,000 red cells per c.mm. As an alternative when only a small sample of blood, e.g. 1 c.c., is available, the

sedimentation rate is measured at the actual cell content, if not below 3,000,000 reds, and the sedimentation rate for 5,000,000 deduced from a standard graph.

All sedimentation rates quoted in this paper are corrected to blood at the standard of 5,000,000 reds per c.mm. The figures give actual mm. falls in one hour at standard room temperature on a column of 32·5 mm. and are not expressed as percentages.

3. The sedimentation rate undergoes appreciable modifications in physiological states, and these modifications should be fully appreciated before an attempt is made to evaluate the influence of pathological conditions upon the sedimentation rate.

(*a*) At birth, and for many months afterwards, the suspension stability is extremely high, the adult sedimentation rate being attained at about the first year of life.

(*b*) Women show a slightly higher sedimentation rate than men, due, probably, to the higher content of haemoglobin and larger size of cell in the former.

(*c*) Menstruation is accompanied by fluctuations of the sedimentation rate; a premenstrual rise in sedimentation rate is followed by a retardation during the menstrual flow, after which a steady rise of sedimentation rate occurs during the resting period until the acme is reattained in the premenstrual phase.

(*d*) During pregnancy the sedimentation rate is augmented; the earliest point at which acceleration is noted is the 10th to 12th week, after which further increase ensues until the maximum is attained at full term.

(*e*) The suspension stability varies in different animals, each having its own characteristic sedimentation rate.

4. The sedimentation test is a most delicate and sensitive reaction which reflects very faithfully the state of equilibrium of the blood in relation to any pathological process. It is not specific for any disease, therefore its uses as a specific diagnostic agent are almost limited to the domain of tuberculosis, where it may be employed in conjunction with a small provocative dose of tuberculin. Used cautiously, however, and as an adjunct to the clinical picture, the S. T., if correctly interpreted, will be found to possess great value and will often weigh down the scales of differential diagnosis. In conditions where there is a suspicion of latent and acute inflammatory processes, accompanied by a normal temperature and leucocyte count, or in obscure carcinomata, the S. T. may be utilized to great advantage, just as, on the contrary, the finding of a normal S. R. excludes an active inflammatory or neoplastic process.

5. Probably the most important use for the S. T. is that of a prognostic agent. It follows very accurately the course and evolution of a pathological process, and repeated tests are of considerable value. Clinical improvement goes hand in hand with a slowing S. R., whereas a fatal evolution is almost invariably accompanied by an increasing rapidity of sedimentation. In any disease,

therefore, the response to treatment can be observed and a vigilance may be maintained upon convalescence.

6. The S. R. was investigated in its application to gynaecology and obstetrics, surgery, and general medicine. It is indicated how the S. T. may be utilized to differentiate between functional and organic lesions, between innocent and malignant conditions—especially of the gastro-intestinal tract—and between inflammatory and non-inflammatory lesions.

7. In paediatrics the S. T. may be employed to advantage, since the finding of a rapid S. R. in the new-born or in the apyretic young infant who may merely show a lack of normal development, will speak for hereditary syphilis, even in face of a negative Wassermann reaction.

It is my pleasant duty to record my indebtedness to the Honorary Staffs of the General, Queen's, and Children's Hospitals, Birmingham, and the Medical Staffs of the Hôpital Cochin, Paris, and of the Wilhelminenspital, Vienna, for permission to utilize the patients under their charge for the purposes of investigation. To Mr. Collier, Pharmacist to the Children's Hospital, my thanks are due for the two photographs.

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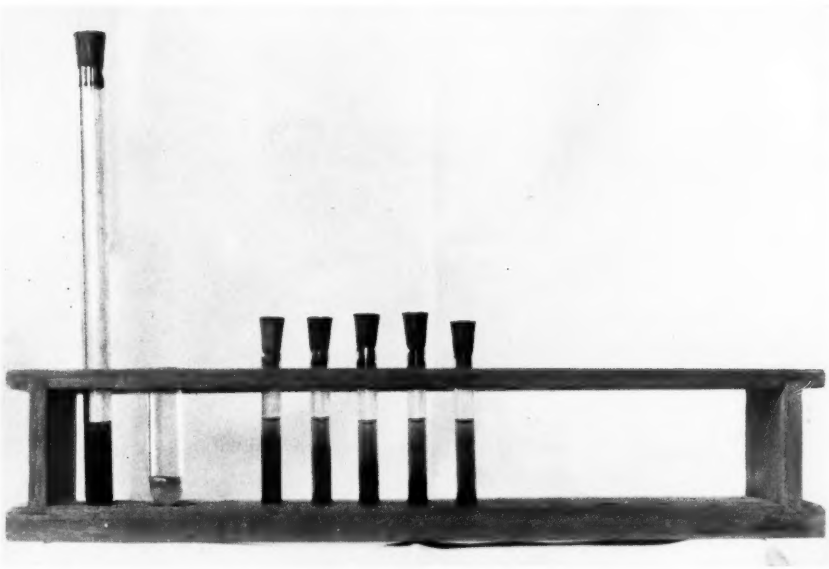

FIG. 1. Sedimentation tubes in special rack. Height of fall of erythrocytes shown at end of one hour.

Reading from left to right the tubes are :–

(i) Large tube containing reserve of blood at a count of 5,000,000 red cells per c.mm.
(ii) Plasma used for diluting purposes.
(iii) Sedimentation tube containing 5,000,000 red cells per c.mm.
(iv) " " " 4,000,000 " "
(v) " " " 3,000,000 " "
(vi) " " " 2,000,000 " "
(vii) " " " 1,000,000 " "

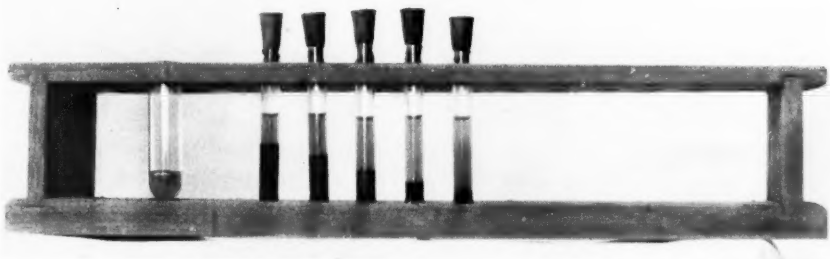

FIG. 2. Photograph showing height of fall attained by the red cell columns at the end of one hour in citrated blood taken from a case of tuberculous adenitis. The concentration of red cells in the tubes is precisely similar to that in the tubes shown in FIG. 1.

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CRITICAL REVIEW[1]

HYPOGLYCAEMIA

By G. M. WAUCHOPE

CONTENTS

	PAGE
History	117
Experimental Hypoglycaemia	
Hypoglycaemia in man prior to the use of insulin	118
Insulin hypoglycaemia	118
Spontaneous hypoglycaemia	119
Blood-sugar Level	119
Variation in severity of symptoms	120
Fatal hypoglycaemia	121
Symptomatology of Hypoglycaemia	121
Pathogeny	126
Morbid Anatomy	129
Spontaneous Hypoglycaemia	
Organic disease of the pancreas	130
Hypertrophy of the islands of Langerhans	131
Functional hyperinsulinism	132
Disease of the suprarenals	134
Pituitary tumours	135
Thyroid dysfunction	136
Pluriglandular deficiency	136
Disease of the liver	136
Muscular wasting	137
Lowered renal threshold	137
Lactation hypoglycaemia	138
Alimentary hypoglycaemia	138
Organic nervous disorders	139
Insulin Hypoglycaemia	139
Hypoglycaemia after the suspension of insulin	147
Diagnosis	147
Prevention and Treatment	150
Danger of accidents	153
Bibliography	153
References	153

History

During the ten years that have elapsed since Banting and Best isolated insulin in 1922, hypoglycaemia has become a familiar clinical syndrome. The order of its discovery was unusual, if not unique, in the history of medicine, for it was first recognized in the exhibition of a new therapy, and was afterwards found to occur as a result of natural causes.

The fact that the blood-sugar may be reduced or absent has been known since 1849, when Claude Bernard, who pointed the way to almost every subsequent discovery about carbohydrate metabolism, demonstrated it in experimental animals. Before the isolation of insulin various experimental means had been found for producing the condition of low or absent blood-sugar. For instance, the glycogen stores of the liver were prevented from

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reaching the general circulation by section of the nerve-supply of the liver (Claude Bernard (1849)); Kaufmann (1895)); by ligature of the aorta and vena cava above the diaphragm (Seegen (1890)); or by excision of the liver (Mann and Magath (1921)).

von Mehring (1889) and Minkowski (1892) produced hypoglycaemia by the administration of phloridzin, which lowers the renal threshold and allows overflow glycosuria; the blood-sugar is reduced and the glycogen of the liver depleted to make good the loss; the condition in experimental dogs is like that in human renal diabetes. Phosphorus poisoning was found by Frank and Isaac (1911) to lower the blood-sugar in rabbits by damaging the liver; a combination of phosphorus poisoning and phloridzin produced severe hypoglycaemia. Underhill (1911) found that hydrazine poisoning had a similar effect; he also lowered the blood-sugar in rabbits by altering the acid base equilibrium through the administration of calcium salts, trisodium phosphate or sodium carbonate (Underhill (1916)).

Removal of the suprarenal glands in dogs reduced the blood-sugar, in the experiments of Bierry and Malloizel (1908), from levels averaging 0·13 per cent. before operation (five dogs) to levels averaging 0·088 per cent., within three and a quarter hours. Porges (1910) obtained considerably lower levels in dogs, which survived longer, for example, 0·033 per cent. nine hours and 0·032 per cent. thirteen hours after the operation.

Hypoglycaemia in man prior to the use of insulin. In man a low blood-sugar had been recognized before 1922 in three distinct conditions.

In 1910 Porges, who was the first to observe hypoglycaemia in man, reported three cases of Addison's disease in which the blood-sugar levels were 0·067, 0·052, and 0·033 per cent. respectively.

Cushing, in 1912, published a case of pituitary tumour, in which the fasting blood-sugar was 0·0394 per cent. Asthenia and pigmentation gave rise to the suggestion that the suprarenals also were involved, but the systolic blood-pressure was 140 mm. Hg.

Joslin, in 1921, published three cases in diabetic patients on the low diets of the Allen era where exhaustion of glycogen reserves was associated with hypoglycaemia. The blood-sugar in one of these cases fell to 0·04 per cent. (Case No. 19).

Thus the biological fact of hypoglycaemia was known to laboratory workers, and had been reported as a rare occurrence in clinical medicine; it was not, however, associated with a definite symptom complex until the results of over-doses of insulin were observed.

Insulin hypoglycaemia. In 1922 Banting and Best found that their extract of the pancreas invariably produced in rabbits hunger, thirst, hyper-excitability and fear, and finally convulsions. As soon as insulin was available for the treatment of diabetic patients similar symptoms were observed in man (Banting, Campbell, and Fletcher (1923)). They constitute a definite syndrome, and insulin hypoglycaemia became familiar both to physicians and to the patients themselves. In Toronto, in the early days, symptoms were

deliberately induced so that patients should recognize them and apply the remedy (Campbell and Macleod (1924)).

Spontaneous hypoglycaemia. The eyes of the profession being thus opened, it was soon perceived that the same symptom complex, associated with a low blood-sugar, occurred in non-diabetic patients and without the administration of insulin. Seale Harris, in October 1923, reported two such cases at a meeting of the Virginian State medical association and named the condition ' hyperinsulinism '. In January 1924 he saw a case in which hypoglycaemia occurred in a patient who, one year before, had had glycosuria. He considered this to indicate an unbalanced action of the islands of Langerhans, ' dysinsulinism '. He reported these three cases with two others in 1924, but in none was the pathological basis verified.

The next important landmark in the history of hypoglycaemia was set up in 1927 by Wilder, Allen, Power, and Robertson, who described an operation at the Mayo Clinic on a patient who had typical symptoms and even convulsions, and whose blood-sugar fell as low as 0·027 per cent.; a tumour of the pancreas was found, with a secondary tumour in the liver from which insulin was extracted (Case No. 2). Thus was established the proof that hypersecretion of insulin can cause hypoglycaemia.

In 1928 an operation was undertaken by Finny and Finny of Baltimore for the relief of similar symptoms; two-thirds of an apparently normal pancreas was removed, but with only slight improvement (Case No. 9).

In 1929 Howland, Campbell, Maltby, and Robinson reported a case in which a carcinoma of the pancreas was excised with complete clinical cure (Case No. 4).

Thus by 1929 spontaneous hypoglycaemia was a sufficiently definite disorder to justify surgical intervention. Unfortunately, in many of the cases the pathology is not clear, for clinical hypoglycaemia has been observed in a number of diverse conditions. It seems opportune now to review the harvest of a decade.

The Blood-sugar Level

Hypoglycaemia, hyperinsulinism (Harris), or glycoprivic intoxication (Fischler) has two aspects: first, the actual low level of sugar in the circulating blood, and, secondly, the associated symptoms.

The amount of sugar in the circulating blood varies under normal conditions both in man and in animals; the effect of insulin in lowering the blood-sugar also varies. The hypoglycaemic action in rabbits is used in the physiological assay of insulin, the convulsion level being estimated at 0·045 per cent., but it is necessary to take precautions to ensure uniform conditions and to calculate an average of many animals.

In man the normal level is different in different persons; in the same person it varies at different times of day and in different states of nutrition. It is lower in children under three than in adults (Spence), and it is higher in old people owing to defective storage and a rise in the renal threshold to about 0·200 per cent. (Marshall).

Variations in the method used for analysis and the source of the blood make reported figures not strictly comparable; titration methods (e.g. Bang and Hagedorn) give lower values than colorimetic (e.g. Benedict and Folin). Joslin (1928) published a table showing the normal values according to seven different methods; the lowest (Bertrand) was 0·070 to 0·110 per cent. and the highest (Lewis-Benedict) 0·096 to 0·125 per cent. The plasma gives slightly higher values than whole blood (Joslin) and arterial higher than venous blood, except in diabetics, where the level becomes equal (Rosenow). Joslin, analysing whole blood, found that readings taken before breakfast in normal individuals were most frequently 0·100 per cent., varying from 0·080 to 0·110 per cent. Sigwald, who used the method of Bertrand and Baudouin on the plasma of venous blood, also considers the fasting level to be in the neighbourhood of 0·100 per cent., and the lower limit of the normal to be 0·095 per cent. The maximum normal level after food is under 0·180 per cent., the so-called renal threshold, above which sugar appears in the urine.

The point at which hypoglycaemia begins is even more difficult to determine than the normal level; it is, indeed, not a point but an elastic zone. Many cases have been reported in which symptoms of hypoglycaemia appeared between 0·090 and 0·080 per cent., e.g. by Weichmann. John reported reactions with even higher values. Sendrail and Planques cite eight authorities who agree that any reading below 0·090 per cent. constitutes hypoglycaemia.

Sometimes a rapid fall in blood-sugar, irrespective of the actual level, seems to bring on symptoms. Payne and Poulton reported a case in a diabetic woman of 46 in whom a fall from 0·320 to 0·280 per cent. regularly produced symptoms. Harrison, on the other hand, observed a fall from 0·328 to 0·053 per cent. in five hours without symptoms. Most observations, however, point to 0·080 to 0·070 per cent. as the usual level for the onset of clinical hypoglycaemia (Fletcher and Campbell; Campbell and Macleod (1925)). But in children the level is lower; Harrison estimated the blood-sugar in children under 12 years of age, in eleven of whom it was less than 0·050 per cent., without symptoms on twenty-eight occasions. The lowest value was 0·028 per cent.

Variation in severity of symptoms. As might be expected from these observations, there is no parallelism between the level of the blood-sugar and the severity of the symptoms. Usually the symptoms are slight or moderate above 0·065 per cent., but severe reactions are sometimes encountered; Labbé (1926) reported two such cases in which the blood-sugar was 0·060 and 0·074 per cent.

Similarly, at the other end of the scale convulsions and coma usually occur at levels below 0·045 per cent., but there are many exceptions. Klein and Holzer (1928), for instance, observed four insulin cases in which the blood-sugar was between 0·033 and 0·047 per cent. without symptoms, while Lax and Petenyi reported twenty-nine cases of hypoglycaemia following hyper-

glycaemia induced by an injection of adrenalin, in which the blood-sugar was under 0·070 per cent. with no symptoms of insulin intoxication; sixteen cases 0·060 to 0·070 per cent., seven cases 0·050 to 0·060 per cent., three cases 0·030 to 0·040 per cent., one case 0·028 per cent. Labbé (1931) reported similarly anomalous cases.

An explanation of these varying results is offered by Popper and Jahoda, who found that when caffeine was administered with large doses of insulin to healthy persons, no hypoglycaemic symptoms appeared, although the blood-sugar curves were the same as in other cases where insulin was given without caffeine and symptoms developed. They suggest that reduction in the blood-sugar alone does not cause symptoms, but that insulin intoxication is due to a component factor acting on the visceral nervous centres.

Even in the same patient the reaction may vary; Harrison instances a case in a baby of fourteen months. On one day there were definite signs with a blood-sugar of 0·044 per cent., and on another no reaction with a blood-sugar of 0·032 per cent. Laroche, Lebourdy, and Bussière report similar variability in an adult case of spontaneous hypoglycaemia; severe symptoms occurred on one occasion with the blood-sugar at 0·066 per cent., while on another day it was 0·058 per cent. with no symptoms.

Fatal hypoglycaemia. There is no fixed point from which recovery is impossible. Death has occurred at levels ranging from 0·065 to 0·015 per cent. (Sigwald); usually the readings are about 0·025 per cent. Labbé (1931) reported a case in a diabetic with cirrhosis of the liver in whom the blood-sugar fell to 0·014 per cent., with recovery from coma after lumbar puncture. Millard Smith recorded a glycaemia in a child of four who recovered.

The following generalization is approximately correct: the normal fasting blood-sugar is about 0·100 per cent.: symptoms of hypoglycaemia appear at about 0·080 per cent.; they become severe at 0·050 or 0·045 per cent., and death may occur with the level in the neighbourhood of 0·025 per cent.

Symptomatology of Hypoglycaemia

The symptoms associated with hypoglycaemia, sometimes called the glycopenic complex (Sigwald), are protean, and Oppenheimer (1927) says that each patient has an individual reaction; nevertheless they constitute a definite picture, derived principally from disturbances of the nervous system. Following J. Wilder, the neurological manifestations may be analysed according to the nerve-group affected.

The vegetative nervous system gives rise to symptoms such as sweating or cold, flushes, pallor, dimness of vision, flickering before the eyes, increase of pulse-rate and blood-pressure; sometimes an increased flow of saliva; occasionally strangury; rarely paraesthesiae.

The central nervous system is widely affected, and symptoms may be produced by disturbance at various levels.

General symptoms are headache and fatigue. The bulbo-pontine system gives rise to disorders of speech such as stammering, difficulty in forming

words, and slow articulation; ocular disturbance such as double vision, nystagmus, inequality of pupils; rarely deafness. The cortico-spinal group comprises paralyses, Babinski's sign, aphasia, agraphia, perseveration, apraxia, motor irritability, inco-ordination, trismus, twitchings and convulsions which may be tonic or clonic, localized or general, and may resemble an attack of epilepsy; occasionally disturbances of smell and taste or paraesthesia of the tongue; rarely incontinence of urine or faeces. To the strio-thalamic system belong tremor, choreiform movements, fibrillary twitching, grimacing, gesticulation, torsion, loud speech, rigor of muscles, atonia and katatonia.

Psychic disturbances are frequent and may be slight, like anxiety, depression, negativism, irritability, querulousness; or bizarre, for instance, excitability, desire to sing, shout or dance, maniacal behaviour; or they may result in dullness and confusion of the understanding and lead to disorientation, slowness of thought, inclination to loiter and dawdle, to give random answers, compulsions, impulsive actions, wandering, fugues, homicide, suicide, amnesia, drowsiness, stupor, coma.

There are in addition other symptoms detailed by Sigwald not directly derived from the nervous system, though they may be ultimately of nervous origin.

Of gastro-intestinal symptoms the most frequent is hunger. Roholm demonstrated in sixteen normal persons that insulin stimulated the secretion of gastric juice; the total amount of secretion and the concentration of pepsin and hydrochloric acid were increased as the blood-sugar fell, for example, from 0·097 to 0·029 per cent. The longing for food thus aroused indicates the remedy for the condition. Occasionally there is disinclination or even disgust for food. Refusal of sugar or chocolate is often merely a manifestation of negativism.

Vomiting is uncommon: Sigwald mentions it in spontaneous hypoglycaemia, especially in children where it may be associated with acidosis; the writer has seen it in a case of insulin hypoglycaemia. The experiments of La Barre and Destrée, who showed that hypoglycaemia provokes strong gastric contractions due to vagal action when the blood-sugar reaches about 0·075 per cent., the pancreatic juice being at the same time diminished, provide a possible explanation of the vomiting. Severe vomiting may, of course, produce hypoglycaemia by depriving the patient of food to meet insulin. Diarrhoea similarly may be a symptom or a cause.

Cardiovascular symptoms, such as tachycardia and extra-systoles, are common and are probably due to sympathetic stimulation. Angina pectoris is more serious and more difficult to account for. It is agreed that insulin is apt to precipitate an attack of angina in persons subject to it, for example, Case 31, and it may even bring on angina for the first time in persons with damaged myocardium, as happened in a case reported by Turner (No. 1)[2]:

[2] For convenience of reference abstracts of the cases quoted are numbered consecutively.

A woman of 58 had experienced slight dyspnoea and palpitation on exertion, her heart being enlarged, with calcification of the aortic arch. She had no cardiac pain until she had an attack of hypoglycaemia in which severe precordial and substernal pain radiated down the inner border of the left arm to the little finger; she had three such attacks and no further hypoglycaemia or angina.

Middleton and Oatway, in 1931, made a careful study of the cardiovascular reactions to insulin shock of eleven diabetic patients, and reviewed the experimental and clinical work so far reported; they noted the tendency for the development of arteriosclerosis in diabetes and emphasized the danger of depriving the heart-muscle of circulating glucose. The most important electrocardiographic change during hypoglycaemia is a decrease in the height of the *T*-wave; the *p*-wave is sometimes diminished and the amplitude of the *R*-wave decreased with increase of pulse-rate.

The blood-pressure usually rises at first and then falls; transitory aortic regurgitation has been observed (Weichmann and Koch (1928 and 1929)). The rise is probably due to the compensatory secretion of adrenalin (cf. the experimental work of Canon, *et al.*).

Respiratory symptoms are not important; dyspnoea sometimes occurs, and occasionally bradypnoea, as in a case published by Rathery and Sigwald where the respirations were five per minute.

Haemorrhages, for instance, haematuria (Lawrence and Hollins; Henderson), haematemesis, cerebral and meningeal haemorrhages (Ehrmann and Jacoby) have occurred during insulin treatment, but were not necessarily due to hypoglycaemia.

The temperature is usually subnormal and may fall considerably with the onset of hypoglycaemia.

Weichmann and Koch (1928) demonstrated that the ocular tension decreases as the blood-sugar falls.

The cerebrospinal fluid contains normally less glucose than the blood; the amount varies between 50 and 75 mg. per 100 c.c. (0·050 to 0·075 per cent.). Sigwald quotes authorities who cite figures as low as 0·040 per cent. and as high as 0·095 per cent. In diabetes and in hyperglycaemia produced by the injection of adrenalin, the glucose in the cerebrospinal fluid rises parallel with the sugar in the blood, but in hypoglycaemia it remains approximately stationary, so that the ratio of the glucose in the blood to the glucose in the cerebrospinal fluid, normally about 2 : 1, becomes less and may even be inverted (Sigwald). Nevertheless the glucose in the cerebrospinal fluid is sometimes lowered in profound hypoglycaemia, for instance, in Case No. 40 of spontaneous hypoglycaemia it was 0·020 per cent., the blood-sugar being 0·040 per cent.

Leucocytosis was found by Klein and Holzer (1927) to occur constantly, but not to run parallel with the severity of the hypoglycaemia. The maximum degree was 35,000 white cells with a relative lymphocytosis, and it was found to be higher in healthy persons than in diabetics.

The more common of these symptoms may be grouped together in stages

of increasing severity, and thus grouped they perhaps offer a more recognizable picture of the condition.

Slight hypoglycaemia, sometimes called the premonitory stage, is characterized by fatigue and lassitude, reluctance to make a physical or mental effort, and indefinite restlessness or malaise; children may become pale and tearful and neither adults nor children can describe their symptoms more exactly than as unpleasant. The blood-pressure is said to fall at this stage.

The second stage is attributable to a compensatory secretion of adrenalin; there is pallor or occasionally flushing, and a cold, clammy perspiration; palpitation of the heart; tremor of the hands; often a sensation of hunger or thirst; the temperature is lowered and the blood-pressure and pulse-rate raised. The most prominent subjective feeling in this stage is fear; the patient is afraid of his symptoms and the palpitation and tremor seem to him much more severe than they are found to be when tested. He also feels unnaturally nervous if he has to face any situation which requires courage; even a mild domestic crisis will unman him. A candidate for an examination had a slight attack and was amazed to find himself thrown into panic by the opening question; his hand shook so that his writing sprawled unsteadily across the page. He presently realized that a scanty lunch had brought about hypoglycaemia, ate a lump of sugar, resumed his usual firm handwriting, recovered his courage, and passed the examination. In children night terrors occur and fits of uncontrollable weeping which are cured instantly by a sweet and by nothing else.

In the third stage the senses become clouded, and the state of the patient often resembles that of alcohol intoxication; he becomes confused and dull, sees double, staggers, speaks thickly and indistinctly, often saying the wrong word, his eyes are glassy, and he is either perverse and sullen or unnaturally cheerful and hilarious. A doctor, in the early days of insulin treatment, was convicted of drunkenness, his plea of hypoglycaemia being disbelieved. He died a few months later of diabetes.

The subjective state is one of bravado; the patient may refuse to take sugar; he wants to see what will happen; it amuses him to see two objects instead of one and to watch one of them slip away to one side. He exhibits negativism in all its forms, and he resents the suggestion that he is suffering from hypoglycaemia. One patient insisted on driving his car home with one eye shut (to obviate the diplopia) rather than eat the chocolate he carried with him.

It is probably in this stage that impulsions, hallucinations, and fugues occur. Oppenheimer (1927) instances several cases. A man who began to undress a hundred yards from the station could not tell how he came there or what he was doing, and allowed himself to be taken home. Another patient mechanically poured milk over his head with a spoon and shortly after began to jactitate so violently that he almost threw himself out of bed. Children are often merely naughty and perverse; they may fly into a sudden rage, scream and kick, and refuse obstinately whatever is suggested.

One stage merges imperceptibly into another, but the fourth may be conveniently characterized as the one in which convulsions and paralyses occur; the degree of paralysis ranges from a transitory weakness, such as a drooping of one side of the mouth, to a profound hemiplegia; consciousness is dim, and the patient often lies in a passive state, apparently able to see and hear, but not appreciating what goes on around him. In children the drowsiness is apt to be mistaken for natural sleep. Convulsions may be preceded by twitchings and contortions, and may remain localized or become general epileptiform attacks with foaming at the mouth and even an epileptic cry.

Children, as in other circumstances, are more prone to develop convulsions than adults, but it is doubtful whether the association with hypoglycaemia is in many cases really one of cause and effect. Griffith, however, reported nine cases in which the blood-sugar was very low, even for children; in the case of a child aged sixteen months, the convulsions always ceased when dextrose was given; the blood-sugar on three occasions was 0·020, 0·028, and 0·036 per cent.

Coma, more or less profound, constitutes the next stage; often the patient can be partly roused; sometimes convulsions and twitching interrupt the flaccid condition; rarely hemiplegia or monoplegia can be detected.

The pupils are moderately dilated and react sluggishly, or not at all, to light. Babinski's sign is usually present and may be unilateral or bilateral.

Memory is lost when consciousness is lost; there is no remembrance of a convulsion, although events before and after may be dimly remembered; impulsions and fugues and actions, performed in somnambulist states, are completely forgotten.

In the last stage coma passes into death. Death from hypoglycaemia during insulin treatment for diabetes is rare in proportion to the number of patients who experience attacks. Sigwald collected twenty-four cases. Death in spontaneous hypoglycaemia is usually due to the underlying cause.

The stages outlined above correspond roughly to the degree of the fall in blood-sugar. The patient may pass quickly or gradually from one stage to another, or may plunge straight into convulsions or coma with little or no warning; this is particularly likely to happen where there is a state of unstable blood-sugar equilibrium.

The condition may be arrested, even without treatment, at any stage, and the patient gradually recover. With the administration of sugar and the return of the blood-sugar to normal all symptoms rapidly disappear; nothing is more dramatic in medicine than the swift recovery of the patient from convulsions, coma or hemiplegia, or from apparent intoxication to a completely normal state. It is comparable only to the relief of asthma by adrenalin.

No permanent harmful effects have been observed after attacks of hypoglycaemia; usually when the patient recovers he is perfectly well. In Case

No. 23 the patient, having been for ten hours in coma, felt energetic and fresh and came down early to breakfast.

Occasionally paralysis or other nervous phenomena last for several days, although hyperglycaemia is produced by treatment; Young observed a case in which hemiplegia persisted for two or three days. In Case No. 37 the patient experienced tingling and numbness of the hands and arms for five or six days after a severe attack; these are exceptions; recovery is usually immediate and always complete if the patient lives.

Pathogeny

It is probable that hypoglycaemia, or the tendency thereto, is inherited; Cammidge and Howard (1930) showed that in mice it is transmitted as a Mendelian recessive character, and Cammidge (1930) found a history of symptoms suggesting hypoglycaemia in the blood relations of 35 per cent. of a series of two hundred patients with spontaneous hypoglycaemia; in forty-eight cases he obtained proof by estimation of the blood-sugar that parents or near relations had also a low blood-sugar; in one instance a daughter, mother, and grandmother were affected.

Hyperglycaemia is a similarly hereditable character in mice, and Cammidge (1928) concluded from the pedigrees of diabetic patients that the defect of carbohydrate metabolism, giving rise to glycosuria, may be transmitted either as a recessive or as a dominant Mendelian character. It is, therefore, probable that further investigation into the families of the subjects of hypoglycaemia will show that it also is a Mendelian character.

Regulation of blood-sugar equilibrium. The fundamental cause of hypoglycaemia is believed to be an alteration in the balance of the internal secretions which regulate carbohydrate metabolism, and in the normal person keep the blood-sugar within certain limits. On the one hand, insulin, the internal secretion of the islands of Langerhans, lowers the blood-sugar, while adrenalin, the internal secretion of the suprarenal medulla, raises it. The secretions of the pituitary and of the thyroid glands play a part on the side of adrenalin, and it is possible that the internal secretions of the ovary and testis and of the parathyroids exert some action on the side of the pancreas. The interaction of these hormones is controlled from a nervous centre probably situated in the pons (Macleod). It is believed that an increased amount of sugar in the blood reaching the central nervous centre stimulates it to activate a secretion of insulin by way of the vagus (Sigwald; Macleod); and that, conversely, hypoglycaemia causes an increased secretion of adrenalin by way of the sympathetics (Burn). The low levels of the blood-sugar sometimes observed after glucose tolerance tests (Stenström (1927); John (1926)) are probably the result of undue stimulation of the insulin-producing mechanism by the sudden absorption of sugar into the blood-stream. It is possible that direct nervous stimulation of the liver to secrete sugar is an auxiliary mechanism set in motion by sudden calls to meet the demand of muscular

activity (Macleod). Himsworth has recently put forward the view that insulin is secreted continuously by the pancreas as an inactive substance, and that an activator which he calls 'insulin kinase' is produced in the liver.

The liver is the main reservoir from which sugar is liberated into the blood by the conversion of glycogen; exhaustion or lack of glycogen stores is therefore a factor in the production of hypoglycaemia. The glycogen stores in the muscles apparently play a subsidiary part (Campbell and Macleod (1925)).

The pancreas is the active member of this combination of agents, for insulin directly lowers the blood-sugar, but how it does so is not completely understood. It was formerly believed that the sugar removed from the blood by the action of insulin was deposited as glycogen in the liver and muscles, but this theory has been shown to be untenable in its simple form, for the increase of glycogen in the liver and muscles is not equal to the loss of sugar; probably an intermediate product is formed. Campbell and Macleod (1925) state generally that insulin creates a vacuum for sugar in the tissues, and more particularly that the tension of free glucose is reduced, so that sugar is removed from the blood; that this is not directly dependent on the polymerization of glucose into glycogen; that it is only partly due to increase in the combustion of carbohydrate. They suggest that the disappearance of sugar is perhaps associated with the reduction of inorganic phosphates which takes place at the same time, and that possibly an organic glucose phosphate is produced; Sigwald suggests additional possibilities viz., that sugar is transformed into fat or protein under the influence of insulin; that glucose α and β are transformed into glucose γ, or that glucose is transformed into lactic acid, which has been observed to increase in experimental animals during hypoglycaemia.

Thus the process by which glucose leaves the blood under the action of insulin is unknown, but it does leave the blood and ceases to be available to the organism. Clinically, conditions which increase the amount of insulin in the circulating blood are the most direct and potent causes of hypoglycaemia; they will be considered in detail later.

An injection of adrenalin directly raises the blood-sugar by a simple release and conversion into glucose of glycogen, particularly from the liver. In man the maximum glycaemia after an injection of adrenalin is reached in about one hour, and the fall to normal is succeeded by hypoglycaemia. When the glycogen stores are diminished or exhausted, adrenalin has no effect on the blood-sugar; it is not certain whether adrenalin also releases the muscle glycogen (Goldzieher (1929)).

Canon and his colleagues (1924), in an experimental study, concluded that the sympathetics and adrenals constitute a protective mechanism for mobilizing the sugar from the liver in hypoglycaemia, and that the convulsive stage of hypoglycaemia is due to the exhaustion of adrenalin or lack of glycogen stores.

There is considerable evidence, though no conclusive proof, that adrenalin is continuously secreted in health (Levy Simpson (1932)), but it is certain that disease or destruction of the suprarenals is often associated with hypoglycaemia. As has been stated, the first observation of hypoglycaemia in man was in cases of Addison's disease; but Addison's disease is due to destruction of the cortex of the suprarenals, whereas adrenalin is secreted by the medulla. Levy Simpson failed to produce any rise in the blood-sugar by injection of cortical extract in cases of Addison's disease, and considers that when it is associated with hypoglycaemia the secretion of the medulla is diminished or absent. Thus there is a lack of the counter-secretion to insulin.

The pituitary plays a complicated part in the regulation of the blood-sugar. On the one hand, pituitrin inhibits the action of insulin and produces rapid recovery if given in hypoglycaemia, and, therefore, tumours which diminish the secretion of pituitrin might be expected to further hypoglycaemia by allowing insulin unopposed action. The mode of action of pituitrin is not clear; it is agreed that it has no direct action on the blood-sugar; there is also evidence to show that it liberates glycogen from storage (Lawrence and Hewlett). But since, on the other hand, pituitrin also antagonizes the glycogenolytic action of adrenalin, it seems improbable that it acts by stimulating the sympathetics. Lawrence and Hewlett conclude that pituitrin has a balancing action on carbohydrate metabolism, and inhibits the action of drugs which tend to change the blood-sugar concentration away from the normal in either direction. It controls both the hypoglycaemia of insulin and the hyperglycaemia of adrenalin, but it effects no appreciable change in a normal blood-sugar concentration. Warren suggests that the influence of the pituitary on carbohydrate metabolism may best be considered as neurogenic.

The matter is further complicated by the association of hypoglycaemia with acromegaly, and J. Wilder put forward the theory that the anterior pituitary has an action on carbohydrate metabolism similar to that of the posterior lobe.

Whatever the mechanism, a certain number of cases of pituitary tumour are associated with hypoglycaemia, and others with glycosuria and hyperglycaemia (Colwell). Atkinson collected 1,319 cases of acromegaly from the literature, in 650 of which the presence or absence of glycosuria was mentioned; it was present in 32 per cent., and absent in 68 per cent.; a high sugar tolerance was observed in two cases.

The thyroid acts in the same direction as pituitrin and adrenalin, that is to say, hyperthyroidism is associated with hyperglycaemia. It is believed to act by making the liver more sensitive to stimulation, and more ready to discharge glycogen as glucose (Joslin (1928)); or by increasing the sensitivity of the central nervous system and thus enhancing the effect of adrenalin (Goldzieher). It follows that myxoedema is apt to be associated with a high carbohydrate tolerance and hypoglycaemia.

The parathyroids act, if at all, on the side of insulin. Extracts of

parathyroid have no effect on the blood-sugar level, but Winter and Smith found that in rabbits injected with a preliminary dose of parathyroid extract convulsions were induced by one-third to a quarter the usual convulsive dose of insulin.

The genital glands have not been proved to have any effect on the blood-sugar, though it has been suggested that their action is vagotonic, that is, on the side of the pancreas, and tends to promote hypoglycaemia. Pillman-Williams and Wills, in the study of blood-sugar curves during pregnancy, found that in many cases the curves became lower as pregnancy advanced. Herold considers that the vagus and the associated glands become more active in the later months of pregnancy and lead to hypoglycaemia. Lesions of the ovaries and testes have not been found in association with clinical hypoglycaemia, except in pluriglandular disturbances.

Conditions in which the glycogen stores are diminished are potential, and even actual, causes of hypoglycaemia; they often intensify the action of insulin: for instance, diseases of the liver in which the reserves are destroyed, vigorous exercise which exhausts them, renal diabetes which eliminates an abnormal amount of glucose, and starvation which prevents replenishment, may produce or augment hypoglycaemia.

Theoretically, interference with the glucose-regulating centre in the pons might cause hypoglycaemia. Rathery, Dérot, and Sterne reported a case in which subarachnoid haemorrhage was associated with acute hypoglycaemia (Case 21).

It is obvious from the foregoing that there is no one cause of hypoglycaemia; the conditions which produce it may be summarized as follows:

1. *Excess of insulin.* Therapeutic injections. Tumours and hyperplasia of the pancreas. Functional hyperinsulinism (idiopathic hypoglycaemia).
2. *Lack of opposing secretions.* Disease of the suprarenal glands. Pituitary tumours: posterior lobe, anterior lobe (acromegaly). Myxoedema.
3. *Lack of glycogen.* Destruction of reservoirs: disease of the liver; wasting of muscles. Abnormal excretion of sugar: renal diabetes; lactation. Active depletion of stores: muscular exercise. Failure to replenish stores: starvation.
4. *Interference with regulating centre.* Nervous disease affecting the pons. Overaction of the vagus.

Morbid Anatomy

The morbid anatomy is that of the primary condition, but since the symptoms are principally derived from the nervous system, the observations of Wohlwill on two cases of death in hypoglycaemic coma are of interest. The patients were diabetics, one aged 62 and the other 29; the first, a woman, had a mammary abscess, and was given 100 units of

insulin each day for three days before admission to hospital in insulin coma; the second died of hypoglycaemia after recovery from diabetic coma. There were no macroscopic lesions in the brain; microscopically there was widespread Nissl's degeneration of the ganglionic cells and an amoebic appearance of the glial cells; in the first case there was also diffuse swelling of the axis cylinders.

Spontaneous hypoglycaemia has now been recognized in some hundreds of cases, and in a large number of conditions; the most important of these is pancreatic hyperinsulinism; Gammon and Tenery, in 1931, made an elaborate analysis of thirty reported cases and included one of their own; in twenty-two of these the origin was considered to be pancreatic. Harris, in 1932, reviewed the reports of about fifty cases from American literature, where the greatest number are to be found.

Organic disease of the pancreas. 1. Carcinoma. Three cases only have so far been reported. Wilder, Allan, and colleagues (1927); Thalhimer and Murphy (1928); Howland, Campbell, and colleagues (1929).

The case of Wilder may be taken as an example (No. 2): A medical man 40 years of age had renal colic in 1924 and glycosuria early in 1925. His blood-sugar was normal, but there were traces of sugar in some specimens of urine; in November 1925 he began to feel faint and weak before meals, especially when he exerted himself; on one occasion he became stuporous after operating; trembling and sweating were prominent symptoms and a curious paraesthesia of the tongue and lips. For more than a year he warded off these attacks by taking frequent meals, and his wife woke him to give him sugar during the night. He had several severe attacks of convulsions and unconsciousness, and on one occasion (March 1926) coma lasted for two hours, and intravenous dextrose had to be given. The attacks became more frequent and more severe, and in September the patient came under observation. Exhaustive investigations were made; on one occasion his blood-sugar fell to 0·027 per cent. four and a half hours after a mixed meal, when he was in a stuporous condition interrupted by convulsive jerks. Epinephrin and pituitrin had no effect in raising the blood-sugar. His blood-pressure was about 110/60 mm. Hg. At operation an inoperable tumour in the tail of the pancreas was found with metastatic nodules in the liver. He died a month later. Histologically both pancreatic and metastatic tumours contained cells resembling those of the islands of Langerhans, and the extract from a large tumour of the liver produced hypoglycaemia in rabbits and was of the strength of 40 units of insulin per 100 grm. of tissue.

The case of Thalhimer and Murphy (No. 3) occurred in a woman of 57 who had had symptoms for two and a half years and latterly epileptiform convulsions; these attacks had no relation to food; the blood-sugar was 0·0355 per cent. a few days before death, the cause being only revealed at autopsy.

The patient treated by Howland and Campbell (No. 4) was a woman of 52, who during six years had attacks of confusion, faintness, and apprehension; she appeared to be intoxicated, perspired freely, and occasionally had a convulsion. The course of the illness was erratic; coma was infrequent, but during one period of unconsciousness the blood-sugar was 0·040 per cent. The case was remarkable in that a small tumour was successfully

removed from the pancreas with complete relief to the hypoglycaemic symptoms; the tumour contained insulin and had the character of a slow-growing carcinoma of the islands of Langerhans.

2. Adenoma of the pancreas, associated with symptoms of hypoglycaemia, has been reported in six cases: McClenahan and Norris (1929) (No. 38); Cushing (1930); Carr, Parker, *et al.* (1931) (No. 5); Smith and Seibel (1931) (two cases); Womack, Gnagi, and Graham (1932) (No. 6). In four of the cases the symptoms were completely relieved and the patients restored to health by removal of the tumour; in the cases of McClenahan and Norris, and one of Smith and Seibel, the tumours were found at autopsy.

The case of Carr, Parker, and their colleagues is typical (No. 5):

A youth of 19, who was attending a military college, came under observation with a diagnosis of epilepsy on account of convulsions and periods of odd behaviour of which he remembered nothing. One morning he heard the bugle sound the reveille and remembered nothing more until he found himself in hospital being examined; meanwhile he had dressed clumsily and had gone to the mess where his inco-ordinated movements in eating had drawn attention to the fact that he was ill. He slept for thirty-six hours in the hospital and woke up feeling well. These attacks became frequent, especially in the late morning; he became hungry, anxious, and confused, and continued, awkwardly, whatever he was doing; one day he drove through crowded streets for three-quarters of an hour with no recollection of it; sometimes stupor, with slight cyanosis and muscular movements, lasted for hours. His blood-sugar was found to be 0·044 per cent. when he was in a semi-conscious state. For six months he tried to ward off the attacks by a diet rich in carbohydrates and by taking sugar when one was imminent, but was not really successful and became more and more tired, till at last, after a severe attack, he consented to operation. An adenoma was resected composed chiefly of β cells, and the patient made a complete recovery.

Womack's case (No. 6) showed a different but equally typical symptomatology. A farmer of 44 used to be confused while out at work before breakfast; he felt as if he had had too much alcohol; one day, about two months from the onset, he was carried into the house unconscious; two months after this his attacks came on before he got up in the morning and were characterized by twitching, confusion, and random speech. He found that taking food in the night prevented the early morning attack, and he always carried sweets about with him in the day. When he came under observation his fasting blood-sugar was 0·050 per cent. and his blood-pressure 128/74 mm. Hg. A small tumour was removed from the pancreas and a clinical cure was effected. The authors were in some doubt, on examining the tumour microscopically, whether it was strictly an adenoma or whether it was feebly malignant, for there was no definite capsule, and normal pancreatic elements were included.

Hypertrophy of the islands of Langerhans. Phillips reported a case of a negro who was found unconscious and whose blood-sugar before death was 0·025 per cent. There was also high blood-urea and at autopsy subacute glomerular nephritis; the pancreas looked normal, but the islands were hypertrophied with an increase in the size of the cells by more than 50 per cent. of the normal, and Phillips thought these findings would account for

the low blood-sugar by an increased production of insulin. Two cases in children born of diabetic mothers, where the islands of Langerhans of the infants were considerably hypertrophied, support his view (Dubreuil and Anderodias; Gray and Feemster). On the other hand, in this case, the renal lesion may have lowered the threshold for glucose and have contributed to the low blood-sugar.

The proof of hypertrophy of the islands of Langerhans with hypersecretion, analogous with hyperthyroidism, is not yet established.

In this connexion the experiments of de Takats *et al.* (1930) are interesting; they produced hyperinsulinism in dogs by trauma to the pancreas (dividing it with a cautery), and thought that hyperplasia and hypertrophy of the island tissue resulted. Allan (1920) found hypertrophic islands in partly pancreatectomized dogs. de Takats and Wilder (1929) divided the pancreas by cautery in a diabetic boy with the object of isolating the caudal end and promoting atrophy of the acinar tissue and hypertrophy of the islands in accordance with experimental results; after recovery from the operation the boy's carbohydrate tolerance was increased.

Functional hyperinsulinism. Acute and chronic idiopathic hypoglycaemia has now been observed in a large number of cases of no definite aetiology in which functional hyperinsulinism has been postulated. Harris (1932) examined the fasting blood-sugar in 1,497 non-diabetics and found sixty-seven cases in which the level was 0·079 per cent. or under, the lowest being 0·045 per cent.; most of these patients, especially those whose fasting level was below 0·069 per cent., had symptoms attributable to hypoglycaemia. The course may be acute or chronic; Moore and his colleagues recorded a case (No. 7) in which the onset was acute and recovery complete with no recurrence during fourteen months:

> The patient was a married woman of 27 who was admitted to hospital in a semi-conscious condition; the next morning she was completely unconscious, slightly cyanosed, with deep, stertorous breathing, and frothing at the mouth. Babinski's sign was positive in both sides, the limbs were rigid, and there was blepharospasm. The blood-pressure was 90/70 mm. Hg; the urine contained a trace of albumin, no sugar, diacetic acid, or casts; the blood-sugar was 0·035 per cent. and the blood-urea 0·060 per cent.; 10 grm. of glucose in 20 c.c. of water were injected into a vein and the patient immediately recovered consciousness; there was achlorhydria, and the stools contained a large quantity of undigested starch.
>
> A year before her admission she had had attacks of dizziness and an inclination to faint before meals; she had had three intravenous injections of novarsenobillon two months before admission, although the Wassermann reaction was negative; three days before admission she had become unconscious for a few moments, and on the day before admission had been unable to recognize her husband.

The authors consider the possibility that the failure to absorb starch was an aetiological factor in this case; under treatment undigested starch disappeared from the stools, and a test meal taken three months later showed

the presence of hydrochloric acid. It is also possible that damage to the liver by novarsenobillon aggravated the condition, but there were slight symptoms before it was administered. There was no recurrence of symptoms, though the fasting blood-sugar remained low (0·062 to 0·078 per cent.), and a blood-sugar curve taken fourteen months after the attack did not rise above 0·082 per cent. The condition was probably 'acute on chronic' hypoglycaemia like that in the case of Laroche, Lebourdy, and Bussiére which was complicated by a polyneuritis, possibly, as the authors suggest, due to prolonged hypoglycaemia. The patient had acute exacerbations with visual disturbance and even unconsciousness, although the blood-sugar did not fall very low (0·058 to 0·066 per cent.).

Chronic mild hypoglycaemia is not rare. Cammidge (1930) analysed 200 cases in which the age of the patients varied from 1 year to over 70; 128 of these had symptoms which improved when the level of the blood-sugar was permanently raised. Chronic infection, especially of the gastro-intestinal tract, was the most frequent exciting cause. In about 50 per cent. a low renal threshold was present, and this, rather than excessive secretion of insulin, is probably the cause in most mild cases; in fifty-one patients the defect appeared to be in the liver, and was in most cases inherited. Recurrent headaches, neurasthenia, lack of energy, and convulsive attacks were other manifestations. Harris's (1924) first cases may be taken as examples of so-called hyperinsulinism, and were described under that title. The symptoms were mild, always came on before meals, and were relieved by taking sweet food. His first patient, a physician of 60 years of age, had been an excessive eater of sweets, and Harris thinks that eating large amounts of carbohydrate may induce hyperinsulinism by stimulating the pancreas unduly. The second patient had a lowered renal threshold, his fasting-sugar being 0·065 to 0·070 per cent., and there were traces of sugar in the urine during a tolerance test, when the blood-sugar level did not rise above 0·167 per cent. The third case (No. 8) Harris believed to be one of 'dysinsulinism':

> The subject was an obese woman who, in 1923, weighed 220 lb. and passed sugar in the urine. A year later her weight was reduced to 160 lb. by dieting, and she began to experience weakness and nervousness at about one o'clock at night relieved by eating. Her blood-sugar during a 'nervous rigor' was 0·047 per cent.

All three patients were relieved of their symptoms by a diet low in carbohydrate and rich in fat taken at frequent intervals.

Partial resection of the pancreas has now been undertaken in four cases with a view to diminishing the secretion of insulin, but hypoglycaemic symptoms were not permanently abolished, nor did the blood-sugar remain at normal level afterwards.

In the case of Finney and Finney (No. 9) the patient was a woman of 53 whose symptoms began four years before, with the menopause, and consisted in periods of confusion and strange behaviour, giddiness, and diplopia

coming on before meals; for eighteen months convulsions had occurred from time to time. The taking of food dissipated an attack but began to lose effect. The fasting blood-sugar was 0·052 per cent. and the sugar in the cerebrospinal fluid 0·034 per cent.; 10 units of insulin provoked a typical attack unless glucose was also injected. Adrenalin raised the blood-sugar to normal. The blood-pressure was 116/80 mm. Hg. Laparotomy was performed, and about two-thirds of the pancreas was removed (22·5 grm.); both macroscopically and on microscopic examination it appeared normal.

Allan operated on two patients: (No. 10) a man of 52 had typical attacks on exertion or if meals were infrequent; symptoms came on when the blood-sugar fell below 0·060 per cent.; the lowest observation was 0·040 per cent. Fourteen grammes of the pancreas were resected with distinct temporary improvement but subsequent relapse (Allan (1929)).

His second patient (No. 11), a man of 47, had periods of excitement in which he sometimes became maniacal, chiefly during the night. At first food relieved or prevented the attacks, which came on when his blood-sugar fell below 0·050 per cent., but he became unable to work. A portion of the pancreas weighing 8 grm. was resected and was histologically normal; the patient was no better (Allan, *et al.* 1930). Holman removed one-third of the gland with amelioration of symptoms but no increase in the blood-sugar (Allan, *et al.* 1930) (No. 11 A).

There are several comments to be made on these cases:

1. The pancreas was normal in each case and, as Finney suggests, the cause of the condition may have been other than hypersecretion of insulin.

2. An insufficient amount of pancreatic tissue may have been removed. Experimentally resection of 90 per cent. of the pancreas in dogs is required to produce glycosuria and hyperglycaemia (Allan (1920)).

3. Allan's first case (No. 10), in which the hypoglycaemia improved and then relapsed, indicates the possibility of compensatory hypertrophy of the remaining normal tissue.

Functional overactivity of the islands of Langerhans is difficult to demonstrate, and it must be admitted that conclusive evidence is so far lacking.

Disease of the suprarenals. Addison's disease is often associated with low blood-sugar, probably in the majority of cases. Levy Simpson found the blood-sugar almost constantly subnormal (below 0·075 per cent.) in every case of six; the lowest values were in the neighbourhood of 0·050 per cent. Rowntree, in nine cases, found a fasting blood-sugar below normal; the lowest level, 0·045 per cent., occurred in two cases. Porges (three cases), Wadi, and many others have reported the association of Addison's disease with hypoglycaemia, which was in most cases incidental. Some of the symptoms of Addison's disease are similar to those of hypoglycaemia: weakness, fatigue in the earlier stages; convulsions, stupor, and unconsciousness in the later.

Wadi's case (No. 12) may be taken as an example in which the lowered blood-sugar seemed to play a real part. A man of 24 became increasingly weak and easily tired and found that he had to eat frequently. When he

was seen two years from the onset he was almost too feeble to stand; there was much pigmentation and a low systolic blood-pressure (70–75 mm. Hg). His blood-sugar was 0·071 per cent. and fell, eight minutes after 2 mg. of adrenalin given intravenously, to 0·051 per cent.; half an hour later it was 0·043 per cent. with hypoglycaemic symptoms. Three days later there was a sudden onset of convulsions, during which the blood-sugar was 0·032 per cent. and the blood-pressure 63 mm. Hg. He was given dextrose and adrenalin and recovered, but had two similar attacks the next day, and died on the fourth day in severe hypoglycaemia, his blood-sugar being 0·033 per cent. At autopsy there was tuberculosis of both suprarenal glands.

One case of suprarenal carcinoma with fatal hypoglycaemia has been reported by Anderson (No. 13). A man of 33 was admitted to hospital semi-conscious; four months before he had temporarily lost the power of speech, and on another occasion he had spoken irrationally; for six weeks he had been easily tired and had had double vision. Two days before admission he could not be roused in the morning and had remained semi-conscious all day, but had recovered and seemed normal for two days. Intravenous glucose restored the patient and transient glycosuria supervened, but he relapsed into a semi-comatose condition with intermittent twitching and periods of excitement, in one of which he developed rigidity of the right arm and in another unilateral Babinski's sign. The blood-pressure was 120/80 mm. Hg and the blood-sugar 0·060 per cent. The patient was given a diet containing large quantities of carbohydrate, and was able to leave the hospital. He was well for three weeks and then became violent, but glucose restored him. Two months later he was again admitted in coma; his blood-pressure was 95/80 mm. Hg and his blood-sugar 0·069 per cent. He was repeatedly given glucose and adrenalin, but died in a few days. At autopsy the left suprarenal contained a tumour weighing 400 grm. which was histologically carcinoma of the cortex. The right suprarenal was small and fibrotic and the pancreas was extremely vascular.

Pituitary tumours. J. Wilder in 1930 published two cases of spontaneous hypoglycaemia in which there were radiological and clinical signs of pituitary tumour; he presented the condition as a new syndrome, 'pituitary spontaneous hypoglycaemia', and considered it to be due to lack of the secretion of the anterior pituitary leading to relative hyperinsulinism. Other cases have been reported. Cushing's patient, already mentioned, p. 118, showed a tendency to gigantism and a very low blood-sugar; Wilder quotes four cases of spontaneous hypoglycaemia associated with proved destruction of the anterior lobe of the pituitary and six with probable pituitary lesions. Oppenheimer (1930, i) reported two further cases of acromegaly with hypoglycaemia, but without symptoms.

Wilder's first patient (No. 14) was a stout woman of 45 who had periods of semi-consciousness lasting for twelve to twenty-four hours. Sometimes she would stare vacantly with open eyes, but with no conscious response; restlessness and difficulties in speech occurred in the morning; Babinski's sign was positive on both sides in an attack and the systolic blood-pressure was low (95–100 mm. Hg); the fasting blood-sugar was found to be 0·020 per cent., and intravenous dextrose cut short an attack at once. The chief signs

of pituitary involvement were obesity, intense headaches, and enlargement of the sella turcica.

His second patient (No. 15) was also a woman, aged 55 years, who had left off eating sugar for three years because she was getting stout; she began to have attacks of odd behaviour before the midday meal, especially if it were late; she seemed in a dream and called to a dead sister; sometimes she had twitching of limbs and became semi-conscious. Her fasting blood-sugar was 0·061 per cent., and during attacks it was 0·050, 0·053, and 0·045 per cent. The taking of sugar immediately relieved the symptoms. Her systolic blood-pressure was high (165–205 mm. Hg). She was obese and of somewhat acromegalic appearance; the X-ray picture suggested a tumour in the sella turcica and there was blurring at the edges of the optic disks.

Thyroid dysfunction. Hypoglycaemia without symptoms is frequent in myxoedema; Sigwald mentions a case in which the level was 0·064 per cent. with basal metabolism – 34 per cent. Holman reported a case in a young girl where there was a rapid fall to 0·040 per cent. with severe prostration after thyroidectomy for Graves's disease. The administration of glucose quickly restored the patient and was again successful in a relapse.

Hyperthyroidism is nearly always associated with a raised blood-sugar, but Sigwald observed two cases of Graves's disease where the level was 0·074 and 0·069 per cent. respectively.

Pluriglandular deficiency. Stenström (1926) reported two cases of hypoglycaemia in women in which the thyroid and probably other glands were reduced in activity. Pettersson reported a similar case, also in a woman, who had defective skin and nails, absence of axillary and pubic hair, amenorrhoea, low basal metabolism, low blood-pressure (90 mm. Hg), and low blood-sugar; in an attack of hypoglycaemia it fell to 0·025 per cent.

Disease of the liver. Several cases have been recorded in which destruction of the liver, and therefore of the glycogen reserves, was associated with hypoglycaemia.

Primary carcinoma of the liver accounted for two cases (Nadler and Wolfer; Crawford).

In the case of Nadler and Wolfer (No. 16), also reported by Elliott, the patient was a coloured man aged 30. A tumour of the liver was found at operation four months before his death; during the last three months of his life he had increasingly frequent and severe attacks of hypoglycaemia during which he felt exhausted, lay down, and lost consciousness; in the later attacks he was delirious; the administration of glucose always promptly relieved the symptoms. There were none of the usual signs of hepatic insufficiency, and the patient died in profound hypoglycaemia (blood-sugar 0·013 per cent.), when he was no longer able to eat and passed from one hypoglycaemic state to another. At autopsy the tumour was found to be a primary liver-cell carcinoma replacing 70–80 per cent. of the liver substance; it contained no glycogen, and the glycogen content of the remaining liver tissue, which showed atrophy and swelling of the cells, was only about 0·8 per cent. of the normal; the tumour cells contained no insulin, and the pancreas and suprarenals appeared normal, so that deficiency of glycogen rather than a relative or absolute hyperinsulinism was presumed.

In Crawford's case, another primary liver-cell carcinoma with severe hypoglycaemia, he estimated that at least 500 grm. of apparently functioning liver tissue remained; he calculated that 300 grm. would be sufficient to carry on the functions of the liver and was in doubt as to the cause of the hypoglycaemia in his case. The glycogen content was not estimated.

Parnass and Wagner recorded the case of a child of 9 (No. 17), the subject of an hepatic tumour, whose blood-sugar showed remarkable instability; fasting, it gave no reaction when estimated by the method of Bertrand and Michael, while after a carbohydrate meal it rose temporarily to 0·40 per cent.; glycosuria appeared and acetonuria, which had been present, disappeared, but only temporarily. An injection of adrenalin did not raise the blood-sugar. Thus an impairment of the storage mechanism was evident.

Acute yellow atrophy similarly destroys the glycogen function of the liver and brings about hypoglycaemia. Rabinovitch reported a case in a woman of 28 whose blood-sugar fell to 0·016 per cent.; autopsy showed extreme destruction of liver cells.

In fatal cases of phosphorus and chloroform poisoning (Bodansky), and of poisoning from arsenical compounds, blood-sugar values as low as 0·035 per cent. have been recorded (Cross and Blackford). MacIntosh recorded a case of phosphorus poisoning in a child of 16 months whose blood-sugar fell to 0·025 per cent. but was restored to normal by repeated injections of glucose. Similarly, in biliary obstruction the blood-sugar may be reduced (Marañon (1930)).

Besides the effects of gross destruction of the liver, it has been observed that mild chronic hypoglycaemia is often associated with hepatic defects, both in children and adults. In Cammidge's series there were thirteen cases of severe recurrent bilious attacks, six of pernicious vomiting of pregnancy, and thirty-two of cyclical vomiting in children. Marañon (1930) also observed the association of hypoglycaemia with cyclical vomiting, and it is now recognized that it probably accounts for the success of glucose therapy.

Muscular wasting. Since destruction of the glycogen stores of the liver is a cause of hypoglycaemia, it is possible that wasting of the muscles similarly deprives the body of glycogen, and McCrudden and Sargeant reported a case which might bear this interpretation. A man of 33, suffering from muscular dystrophy, had a morning blood-sugar of 0·073 per cent. which fell, after sixteen hours fast, to 0·064 per cent. After treatment the muscular power improved and the fasting blood-sugar became successively 0·080 and 0·094 per cent.

Lowered renal threshold. Reference has been made to Cammidge's observations which show that lowering of the renal threshold, which permits abnormal elimination of glucose, is common in cases of chronic hypoglycaemia. Labbé (1924) reported details of four cases, in one of which there was a family history of disturbance of carbohydrate metabolism, the patient being the son of an obese father and grandson of a diabetic. Neilsen

studied fifteen subjects of vagotonia who had hypoglycaemic reactions; seven of these had glycosuria of the renal type. The majority of patients with low renal threshold experience slight symptoms or none at all, but on several occasions symptoms have been provoked by the glucose tolerance test, at the end of which the blood-sugar fell below the fasting level; for example, Weill and Laudat reported a case in which the blood-sugar was 0·086 per cent. before the test, 0·107 per cent. at the peak of the rise, 0·048 per cent. at the end of two hours, 0·059 per cent. at three hours, but only slight symptoms occurred. Gibson and Larrimer also induced symptoms on two out of three occasions in the same patient, when the blood-sugar at the end of each test fell below the fasting value: for example, from 0·070 to 0·062 per cent.

Lactation hypoglycaemia. Lactation is a possible source of hypoglycaemia by draining the circulating glucose from the mother's blood. Widmark showed that the blood-sugar of cows is reduced during milking and is restored to normal in about twenty minutes; in women also he found a reduction, but without symptoms, the lowest observed fall being from 0·12 to 0·070 per cent.

(*Case No. 18.*) Stenström (1926) reported symptoms in a woman of 40 who was suckling a child; they were induced by a diet of fat and vegetables which was prescribed for other reasons; she had hunger, cramping pains in the stomach, tremor, and sweating; later, convulsions and stupor; on the three days of this diet the fasting blood-sugar, which had been 0·080 per cent., was 0·050, 0·040, and 0·050 per cent.; when the child was weaned there was no return of the symptoms on the same diet; this patient had pulmonary tuberculosis, which may have made her unduly susceptible to loss of glucose.

Alimentary hypoglycaemia. Starvation certainly plays a part in the production of hypoglycaemia, though it is doubtful if it is sufficient to produce symptoms in perfectly normal persons; pure alimentary hypoglycaemia is as questionable as pure alimentary glycosuria. Harris (1924) tested four patients who were 'literally starving to death', three from carcinoma of the oesophagus, and one from pyloric stenosis; there were no symptoms attributable to hypoglycaemia, and the fasting blood-sugar readings were within normal limits.

Starvation is an important factor in bringing about terminal hypoglycaemia in diabetic patients not on insulin; Joslin (1921) described three cases treated by under-nutrition, two of which were fatal. The first is a good example (No. 19).

The patient, a man of 38 years of age, had had diabetes for three years. The blood-sugar was 0·36 per cent. and acidosis was present. After four days of under-nutrition (total diet for the four days 900 calories) and two days of rigid fast the urine was sugar free and the blood-sugar 0·29 per cent. Small amounts of protein and fat were given, but no carbohydrate, and on the thirteenth day the blood-sugar was 0·050 per cent., the next day the patient was disorientated for an hour, and on the fifteenth day coma

developed unassociated with acidosis and he died in a few hours, the blood-sugar being 0·040 per cent.

Attempts have been made to lower the blood-sugar by means of a ketogenic diet containing little carbohydrate.

Inger Schröder (No. 20) gave an experimental diet of fat and vegetables to a woman medical student of 23 years of age. The diet consisted of F. 226, C. 20, P. 24 on the first day and was gradually reduced to F. 175, C. 13, P. 13 on the fourth. The subject carried out her normal active work and was greatly fatigued; she experienced tremors, nausea, palpitation of the heart on slight exertion from the second day; on the evening of the fourth day she was unusually somnolent, and on the fifth morning, after drinking a large quantity of water, she became semi-conscious; there was air hunger and acetonuria. Twelve grammes of sugar immediately dispelled her symptoms. Before the test the fasting blood-sugar was 0·094 per cent., and it gradually fell, the readings being 0·061, 0·045, and 0·052 per cent. on the last three days.

In this case exercise was probably a contributing factor, and it is possible that the symptoms were due to acidosis, which is, as Marañon points out (1930), often associated with hypoglycaemia. Begtrup and Rosling gave similar diets, and in normal persons produced only slight acidosis and slight lowering of the blood-sugar.

Organic nervous disorders are not, as a rule, associated with hypoglycaemia, although theoretically a lesion in the neighbourhood of the sugar centre would cause it. Rathery, Dérot, and Sterne studied a case in which Sigwald considers that a biological hypoglycaemia (i.e. without symptoms) was caused by a meningeal haemorrhage (No. 21).

A man 43 years of age was brought to hospital in coma. In the afternoon he had experienced a sudden headache, followed by tonic convulsions, with opisthotonos which persisted after admission. A lumbar puncture indicated meningeal haemorrhage with early haemolysis. On the third day, when the convulsions had ceased, the blood-sugar was found to be 0·054 per cent., on the fifth day it was 0·094 per cent., and for several weeks afterwards was unstable.

Oppenheimer (1930) gives a blood-sugar curve in a patient in the post-encephalitic state: after a swift rise to 0·140 per cent. it fell to 0·051 per cent.

Incidental hypoglycaemia has been reported in many diverse conditions, for example, in dementia praecox (Targowla *et al.*), neurasthenia (Nielsen), oedema (Jansen), chronic endocarditis (Goldberg, quoted by Sigwald), bronchial asthma (Malone), mumps (Mironesco, *et al.*); finally, in twelve out of thirty-three unselected, dying, patients, Schmidt and Carey demonstrated terminal hypoglycaemia of from 0·028 to 0·075 per cent.

Insulin Hypoglycaemia

By far the most common cause of hypoglycaemia is insulin injected for the treatment of diabetes; among the thousands of patients taking insulin slight symptoms of hypoglycaemia are not uncommon, and probably occur in the

majority of cases, but severe reactions are comparatively rare, especially when one considers the variability of diet and activity, the swift fall in the blood-sugar that may follow a dose of insulin, the changing susceptibility of the body, and lastly the vast possibilities for human error.

Even in patients on well-balanced diet and insulin there are certain circumstances in which hypoglycaemic accidents are likely to occur.

After the first few weeks of insulin treatment, especially in severe cases, the tolerance for sugar increases with the disappearance of acidaemia and gain in weight. If the dose of insulin is not reduced when the urine has been sugar-free for a few days, hypoglycaemia is likely to occur.

During any infection, even the common cold, sugar tolerance decreases, and larger doses of insulin are needed; in severe infections, such as carbuncles and influenza, the increase in dosage may be considerable. Hypoglycaemia occurs with recovery unless the insulin is quickly reduced.

Diabetic patients on balanced diet and insulin often have slight or moderate symptoms if they miss a meal, or even if it is unduly delayed.

Acute gastritis or enteritis, which eliminates the food before it is absorbed, acts in the same way. Two of the reported fatal cases were initiated thus. In one case the diarrhoea was severe and the autopsy revealed pancreatitis (Joslin (1928)).

In the other (No. 22) the patient reduced his morning dose of insulin to 10 units (he was on 40 units a day) on account of diarrhoea and sickness, but he took no food until he felt hypoglycaemic symptoms, when he ate an orange and telephoned to his doctor; he died before assistance could arrive (Campbell and Macleod (1924)).

Vigorous muscular exercise may bring about hypoglycaemia in the normal person, but probably only in exceptional circumstances. Levine and his colleagues estimated the blood-sugar of eleven Marathon runners in 1924: five examined before the race were within the range of normal, but six who finished in bad condition had blood-sugar levels below 0·065 per cent. at the end. They showed symptoms attributable to hypoglycaemia, such as pallor, tremor, asthenia; and the man whose blood-sugar was the lowest (0·045 per cent.) was carried in prostrate. The winner, on the other hand, who broke the world's record, finished with a blood-sugar of 0·089 per cent.; he and four others, whose blood-sugar was above 0·080 per cent. after the race, were in good condition.

In diabetics on insulin, exercise often precipitates hypoglycaemia; Lawrence (1926) described two cases in which this was very clearly demonstrated and confirmed by experiment on one of the patients, a young man, who, under similar conditions, carried out strenuous exercise on one of two days and on the other day took no exercise. On the first day he experienced severe hypoglycaemic symptoms, and his blood-sugar fell from 0·161 per cent. fasting to 0·051 per cent., while on the non-exercise day he had no symptoms and his blood-sugar remained above 0·181 per cent. It is to be noted that on the day following the exercise there was a recurrence of hypoglycaemia,

in spite of reduced insulin. The following case (No. 23) illustrates several of the conditions predisposing to hypoglycaemia:

A strong, healthy diabetic of about 40 years of age, who had been on insulin for four years, and for the last two years had taken the same dose (30 units a day, in two doses) went to the Pyrenees for a holiday. He had a long day on a mountain without mishap, and two days later undertook a severe twelve hours' climb. During the last part of the descent he had an attack of hypoglycaemia, which caused him to lose his footing and fall. He ate chocolate, but had to be helped down the remaining distance. During the night he was attacked by diarrhoea, and the next day ate little and took no insulin: on the third morning he took half his usual insulin (10 units) and a full diet, and spent a long but easy day riding a mule. In the evening he took his usual insulin (12 units) before dinner, but at the end of the meal had a slight convulsion; he was given sugar and chocolate, but soon could not swallow; he spoke slowly and thickly and was able to stagger upstairs with support. He was put to bed half-conscious and almost immediately fell into deep coma; he could not be roused and did not feel the prick of a hypodermic needle. Adrenalin had no effect, but ten hours after the onset (i.e. at 6 a.m.) the patient became conscious and soon recovered completely. He took no insulin that morning and 6 units in the evening, and had slight symptoms at 11 p.m.

This case is instructive on several points: the patient had been perfectly well for a long time on a settled dose of insulin until the glycogen reserves were exhausted by hard exercise; secondly, although diarrhoea prevented the immediate replenishment of glycogen, on the day of the attack the patient ate plenty of carbohydrate food and took no excessive exercise, yet there was no glycogen reserve, as was shown by the failure of adrenalin. The insulin taken before the final meal acted before the food could be absorbed, and chocolate and sugar failed to avert coma, although usually sweet food relieved the symptoms immediately. Recovery was presumably due to the eventual absorption of this food. In spite of reduction of insulin from 30 to 6 units he had slight hypoglycaemia on the following evening, so that even then glycogen had not accumulated; it is probable that insulin, with large amounts of carbohydrate, should have been given during and after the day's climb.

In cases of severe diabetes an especially dangerous time for the onset of hypoglycaemia is *after recovery from diabetic coma*, the large doses of insulin employed to get rid of the hyperglycaemia and acidaemia seem to exert a cumulative action, and it needs considerable experience to reduce the dose in time to prevent an excessive fall. Among twenty-four fatal cases of hypoglycaemia after insulin collected by Sigwald the greatest number (seven) followed diabetic coma.

In two cases the onset of hypoglycaemia was sudden, and the patient passed almost directly from diabetic to insulin coma.

One patient (No. 24), a woman of 29, was brought to hospital in diabetic coma (blood-sugar 0·462 per cent.); she received 135 units of insulin the 1st

day, 70 the 2nd, and 90 on the 3rd and 4th. She recovered from the diabetic coma and then suddenly lost consciousness; her blood-sugar was found to be 0·065 per cent., and she died soon after; at autopsy there was no obvious cause of death (Wohlwill).

In the case (No. 25) of a man reported by Holten, who died in hypoglycaemia twenty-four hours after the injection of only 60 units of insulin, when diabetic coma was threatening, the patient seems to have been unusually susceptible to insulin. (Quoted by Sigwald.)

Similarly, in a case reported by Beck (No. 26), a man of 48 was successfully treated for diabetic coma (blood-sugar 0·401 to 0·609 per cent.); two days after being sugar-free he developed hypoglycaemic coma after an injection of 15 units of insulin; his death was so sudden that sugar could not be given in time.

It seems probable that the glycogen stores are diminished by the failure of carbohydrate metabolism before and during diabetic coma, and that when insulin has reduced the blood-sugar to normal, there are no reserves to meet an excess of insulin. Hypoglycaemia may develop in advanced or terminal diabetes without insulin and merely from exhaustion of glycogen; it is then associated with *Acidosis*. Marañon (1930) points out that when sugar cannot be stored, insulin accentuates the acidosis by increasing the deficiency of glucose, and at the same time it produces hypoglycaemia; if glucose is given with insulin these results are obviated.

Inanition similarly reduces the glycogen stores, and in two fatal cases, one a diabetic and one a non-diabetic, death from insulin was preceded by inanition.

The first was reported by Woodyatt in 1922, when the starvation treatment of diabetes had not been superseded by insulin (No. 26). The patient was received in a state of extreme inanition and weakness and had no glycosuria; he was given a largely increased diet and a calculated dose of insulin; he developed convulsions with a blood-sugar too low to read; sugar was given and produced hyperglycaemia and gross glycosuria, but the patient died without regaining consciousness. The second case (No. 27) occurred in a woman of 27 suffering from Pott's disease of the spine and a calcified tuberculous lesion at the right apex; this patient refused food for three days, and for a further three days vomited persistently and developed acidosis. Insulin, 50 units, was given with 250 c.c. of isotonic glucose solution subcutaneously. On the following four days she received 30 units of insulin with the same glucose subcutaneously and a litre per rectum; she was also given 2 mg. of adrenalin each day. On the 4th day she suddenly became comatose; acetonuria was still present; insulin, 90 units, with 500 c.c. of subcutaneous glucose and 125 c.c. of 3 per cent. bicarbonate of soda was administered intravenously. The next day she was in profound coma with very slow respiration and severe nervous symptoms; there was neither sugar nor acetone in the urine, and the blood-sugar was 0·020 per cent. Intravenous glucose relieved the convulsions, and the blood-sugar rose to 0·149 per cent.; but the patient relapsed and died a few hours later in spite of more intravenous glucose (Sigwald).

In both these cases the lack of stored glycogen was probably the main factor; in the second case the adrenalin which was given in the early stages

would further deplete the stores; the patient may also have been hypersensitive to insulin by reason of her tuberculous lesion. In view of Underhill's experiments, the sodium bicarbonate given intravenously probably accentuated the hypoglycaemia.

Instability of the blood-sugar is a very troublesome condition generally occurring in severe cases and in emaciated patients whose store of glycogen is diminished. It becomes almost impossible to preserve the mean between hyperglycaemia and hypoglycaemia ; a dose of 20 or 30 units before an ample meal reduces the blood-sugar from the neighbourhood of 0·30 per cent. to hypoglycaemic level before the next meal. Brucke instanced the case of a child of 8 who had seven severe hypoglycaemic reactions in less than a month, although her diet and insulin were under strict supervision.

In another child of the same age the fasting blood-sugar was 0·265, 0·190, 0·080, and 0·024 per cent. on different mornings, although the diet and insulin were unvaried (Heimann-Trosien and Hirsch-Kauffmann).

In one of the fatal cases (No. 28) this state of unstable equilibrium was set up. The patient, a woman of 25, was a severe diabetic, needing 50 to 60 units of insulin a day. Within fifteen days she was twice in diabetic coma (blood-sugar on the second occasion 0·450 per cent.) and twice in hypoglycaemic coma. The first of the hypoglycaemic attacks was aggravated by an injection of 40 units of insulin under the mistaken diagnosis of diabetic coma ; the blood-sugar was 0·043 per cent. during eight hours of unconsciousness which ensued, and a few days later diabetic coma supervened, the blood-sugar having risen to 0·450 per cent. It was ten days after this that the second and fatal attack of hypoglycaemia developed when the patient was receiving 40 units of insulin a day (Winogradow and Steinberg).

Hypoglycaemia itself exhausts the glycogen and predisposes to another attack, even if the blood-sugar has risen in the meanwhile. Frequent small doses of insulin afford the only means of attaining an approximately normal blood-sugar, and if this is impracticable it is safer to allow a high level.

Certain complications induce a supersensitiveness to insulin; one of the most important is phthisis. It has been suggested that the great sensitiveness to insulin shown by the subjects of tuberculosis may be due to mild protein shock (*Lancet*, 1929). Two fatal cases occurred in Sigwald's series. The first was reported by Rosendahl (No. 29).

A man of 58, who had been dieted for two months for diabetes, was found to have tuberculosis of the lungs. He was very thin, and his fasting blood-sugar was 0·142 per cent. He was given a low diet, and was sugar-free, but in order to increase his diet to P. 45, F. 103, and C. 18·5, he was given 2 units of insulin each morning; the fat and protein of the diet were increased (P. 65, F. 212), and on the sixth day of insulin treatment his fasting blood-sugar was 0·087 per cent. He received his insulin as usual, and an hour later palpitation, sweating, and weakness came on. He ate 20 grm. of bread with 10 grm. of glucose, but coma developed ; he recovered after 60 c.c. of a 20 per cent. solution of glucose had been given intravenously ; the insulin was discontinued, but three days later the blood-sugar was 0·054 per cent. with symptoms of hypoglycaemia ; glucose was again

administered intravenously and by mouth, and he recovered temporarily, but relapsed in the evening. The next morning his blood-sugar was 0·050 per cent., and in spite of a diet containing 47 grm. of carbohydrate it fell in the evening to 0·036 per cent. It became impossible to raise the blood-sugar permanently, although glucose and other carbohydrate was given freely by all methods, and he died three days later.

At autopsy both lungs were found to be tuberculous, the pancreas was cirrhotic, and there were calculi in the ducts; no glandular tissue was found, and no islets of Langerhans; the liver showed early cirrhosis and a thickened capsule.

In this case there were several conditions which may have caused or contributed to the hypoglycaemia: tuberculosis of the lungs, which may have made the patient unduly sensitive to insulin; cirrhosis of the liver, which may have lessened the capacity to store glycogen; emaciation, which further deprived the patient of glycogen, and a diet poor in carbohydrate.

It is noteworthy that the dose of insulin was extremely small—2 units a day, and that it had been suspended for three days before the fatal attack of hypoglycaemia developed.

The second tuberculous patient (Case No. 30) was a man of 30 who was admitted to hospital in 1924 with 16 per cent. of sugar in his urine, marked acidosis, and a blood-sugar of 0·357 per cent. His blood-sugar fell in four days to 0·090 per cent., but his insulin was increased from 0·5 cm. to 1 cm. to meet an increase of diet to P. 90, F. 60, C. 30. He had a hypoglycaemic convulsion, and insulin was suspended while carbohydrate intake was increased. Two days later he became excited and then semi-comatose, with nystagmus, absent reflexes, ankle clonus, and Babinski's sign; his blood-sugar was 0·027 per cent. 10 c.c. of 5 per cent. glucose was given intravenously, and repeated injections of adrenalin, but he died after being for five hours in coma.

Tuberculosis of both lungs was found at autopsy, and there was glycogen in the muscles and liver (Pemberton).

Here, as in the previous case, the diet was low and the patient was undernourished (weight 91 lb.).

Angina pectoris, arteriosclerosis, and severe heart disease are conditions in which it is agreed that the giving of insulin is dangerous. Joslin (1928) reported three cases in which death occurred; in one of them (No. 31), the sequence seemed clear:

A man who had mild angina for years died in a typical attack four days after beginning insulin treatment; no infarction was found at autopsy, but the coronary arteries were calcified and almost occluded.

A woman of 70 was brought to hospital in hypoglycaemic coma, her blood-sugar being 0·030 per cent.; she died in spite of intravenous glucose, and at autopsy a fresh infarct was found in the heart.

Gigon refers to a patient with gross disturbance of the cardiovascular system who died after the third injection of insulin.

Nicely and Edmondson mention two cases in which heart failure developed in association with hypoglycaemia. One patient with acute failure, tachy-

cardia, prostration, and pulmonary congestion, recovered after prolonged rest and the use of orange juice with reduced insulin and digitalis; the second had auricular fibrillation and recovered completely with the same treatment.

Certain conditions, which when severe are the basis of spontaneous hypoglycaemia, may in lesser degree intensify the action of insulin, for instance, in diseases of the liver such as cirrhosis, which do not entirely destroy its function, very small doses of insulin produce hypoglycaemia, and it is possible that the sensitivity of patients with severe cardiac disease and loss of compensation is due to engorgement and functional impairment of the liver. In these cases it is the lack of capacity for glycogen storage which is the most important factor (*Lancet*, 1929).

Cirrhosis of the liver was probably at least a contributory factor in a case reported by Campbell and Macleod (1925) No. 32:

A man, a chronic alcoholic, took no breakfast one morning although he had his usual 30 units of insulin. He spent an active morning, ran for a train at midday, and was taken unconscious to hospital where he died.

Addison's disease, even when not associated with hypoglycaemia, renders the individual extremely sensitive to insulin; great care must therefore be exercised in using insulin, either to increase the weight of emaciated patients with Addison's disease, or in those cases where diabetes and Addison's disease occur concurrently. Marañon (1925) cites two cases in which small doses of insulin given with ample carbohydrate produced severe hypoglycaemia:

The first patient (No. 33), a woman of 21, suffering from acute Addison's disease, died about two hours after an injection of 5 units of insulin. The second patient (No. 34), a woman of 40, had typical Addison's disease with pigmentation; she was given 10 units of insulin which produced alarming symptoms of hypoglycaemia, with a fall of blood-sugar from 0·160 to 0·044 per cent., and a fall of diastolic blood pressure to 20 mm. Hg.

A curious case (No. 35) was reported by Gellerstedt and Grill, who thought that pituitary changes may have made the patient unduly susceptible to insulin.

A man, 30 years of age, was said to be suffering from diabetes mellitus and diabetes insipidus combined. The evidence for diabetes mellitus was a high blood-sugar (0·261 per cent. when first observed, and later 0·334 per cent. with symptoms of diabetic coma), and sugar and acetone in urine. The evidence for diabetes insipidus was polyuria with low specific gravity (up to 12,000 c.c. in twenty-four hours. Sp. gr. 1,003). Autopsy revealed enlargement of the posterior lobe of the pituitary, and a 'peculiar heteromorphous composition of the cyst colloid of the pars intermedia as well as rarefaction of the colloid appearing as free droplets'.

The patient had been for some time on a liberal diet with 32 units of insulin a day, the blood-sugar varying between 0·180 and 0·100 per cent., when 'the catastrophe broke like a bolt from the blue' on June 22.

That evening his blood-sugar was 0·134 per cent. and he had 12 units of insulin as usual, and at about midnight a hypoglycaemic convulsion occurred which was checked by the administration of sugar by mouth, and adrenalin intramuscularly. The next morning he was free from symptoms, so, although his blood-sugar was only 0·086 per cent., he was given his usual 20 units of insulin; at 10 o'clock he suddenly lost consciousness, and his blood-sugar fell to 0·026 per cent. Nervous symptoms were marked, epileptiform attacks, trismus, bilateral Babinski's sign, and non-reacting pupils. He was twice given glucose per rectum (200 c.c. of a 5 per cent. solution) and adrenalin, but his blood-sugar only rose to 0·031 per cent., and he died three hours after the onset of coma.

In some cases of diabetes a lowered renal threshold develops, and there is hypoglycaemia, although glycosuria persists.

Leyton (1929) reported a case (No. 36) in a child of five and a half years who had been in diabetic coma and had required insulin; this had been suspended but resumed on account of infection; it had been gradually reduced from 36 units a day to 16, when severe hypoglycaemia developed and persisted for ten or eleven weeks with no further insulin; symptoms ceased after seven weeks, but the fasting blood-sugar was 0·060 per cent., although the diet was liberal in carbohydrates. Glycosuria was present throughout, and the renal threshold was low.

Lowered renal threshold probably accounts for some of the cases of unstable blood-sugar already discussed. The following case (No. 37) affords an example.

A woman of 56, who had been treated for diabetes for five years, was admitted to hospital in diabetic coma on five occasions, and each time had had symptoms of hypoglycaemia about a week after recovery from coma; one of these attacks was severe and the patient was unconscious for four and a half hours with Cheyne Stokes's breathing. On the preceding days the blood-sugar was 0·360, 0·374, and 0·236 per cent.; the insulin had not been increased on the day of the attack, which occurred at 11 p.m., and sugar was constantly present in the urine. The patient had persistent albuminuria, and an intermittent *B. coli* infection of the urinary tract, which may have provided the pathological basis for the permeability of the kidneys to sugar, and it was when she was admitted for observation of the renal condition that the lowered threshold became evident. In a tolerance test 1·600 per cent. of sugar was present in the urine with a maximum blood-sugar of 0·112 per cent. During five weeks no day passed without sugar being present in at least one specimen of urine, and yet moderate hypoglycaemia occurred on five occasions. The diet provided about 1,650 calories with 100 grms. of carbohydrate, and the insulin was gradually reduced from 20 units morning and evening to 15 units morning and evening: the highest fasting blood-sugar was 0·262 per cent., and the lowest 0·068 per cent. Hypoglycaemic symptoms occurred on days when the fasting blood-sugar was not at its lowest, for example, 0·143 and 0·162 per cent., whereas on the day when it was 0·068 per cent. there were no symptoms; there was often only a trace of sugar in the urine on days with no symptoms and more sugar on the hypoglycaemic days.

Ignorance and carelessness have on more than one occasion had a fatal result. One patient, who had twice been treated in hospital for diabetic coma, the last time ten days before her death, thought it was threatening

again and gave herself insulin every hour during the night—120 units in all. Glucose was given in large doses, but she died (Joslin (1928)).

Another death (Case No. 38) was due to a mistaken diagnosis, and 20 units of insulin were given when the patient was already in hypoglycaemic coma; the next day he was in deeper coma with paresis in sequence of one leg, both legs, one arm. His blood-sugar was restored by repeated injections of glucose, and indeed reached 0·220 per cent., but he died on the third day (Chabanier *et al.*).

Hypoglycaemia after suspension of insulin treatment. A few cases have been described in which fatal hypoglycaemia occurred some days after the last dose of insulin.

Jonas described a case (No. 39) in which a man of 50 had an operation for gangrene of the feet and was given 5 units of insulin at first three times and then twice a day; he refused his breakfast one day and 'insulin shock' occurred (blood-sugar 0·063 per cent.), and the insulin was suspended. Eleven days later he became delirious, his blood-sugar was 0·030 per cent., and he died in spite of the administration of sugar.

This case occurred in the days of low carbohydrate diet, and is probably analogous to the cases of terminal hypoglycaemia in untreated diabetes. In the tuberculous patients (Nos. 29–30) the insulin had been suspended for three days and two days before the onset of hypoglycaemia.

Diagnosis

The diagnosis is to be considered under two aspects:

In the *non-diabetic* the great diagnostic criterion is the time of the onset of symptoms, viz., early in the morning or before meals, and the almost immediate relief after taking food. Even if the symptoms themselves do not seem to fit in exactly with those described, and even if the patient's disability amounts only to weakness and fatigue, this definite relationship to food is enough to warrant an estimation of the blood-sugar which will clinch the diagnosis.

As may be supposed from the list of symptoms many conditions simulate hypoglycaemia.

Organic nervous diseases, such as those due to cerebral vascular thrombosis, which give rise to hemiplegia or coma are obvious difficulties, but the paralyses of hypoglycaemia are generally transient.

Cerebral tumour was the first diagnosis in a case reported by Womack, Gnagi, and Graham (No. 6) of a man of 44 who had attacks of mental confusion, loss of memory, and transient loss of consciousness. He proved to have an adenoma of the pancreas and spontaneous hypoglycaemia. All his symptoms disappeared after excision of the tumour.

Encephalitis was considered a possible diagnosis and a lumbar puncture was performed in the case of McClenahan and Norris.

(*Case No. 40.*) A man of 41 was brought into hospital unconscious and regained consciousness in an hour and a half. The next day, however, he was again in coma and his blood-sugar was 0·040 per cent., while the sugar in the cerebrospinal fluid was 0·020 per cent. A history was obtained of attacks of loss of memory during the past six months, lasting about an hour and a half and recovering after food. Glucose by mouth, per rectum, and intravenously was unavailing: broncho-pneumonia developed and the patient died. The blood-sugar on the three days during which the coma lasted was 0·040, 0·042, and 0·038 per cent. At autopsy an adenoma of the pancreas was found.

Epileptiform attacks may be indistinguishable from true epilepsy; for instance, in the case reported by Carr and others (No. 5), and even more dramatically in three cases described by Nielsen and Eggleston in which typical epileptic fits began between the ages of 20 and 30 years; one patient had more than 100 attacks of grand mal and many of petit mal; in each case the blood-sugar was found to be low, and a régime, which included frequent feeds and the administration of suprarenal extract by the mouth, abolished the attacks; one of the patients neglected his early morning glass of orange juice and an attack of major epilepsy occurred. The blood-pressure in one of the cases was low at the outset (98/58 mm. Hg) and was raised to 112/66 mm. Hg during treatment; the curve of the glucose tolerance test also rose to higher levels. Four of Cammidge's cases of chronic hypoglycaemia were believed to be suffering from mild epilepsy (1903).

Hypoglycaemia has been recorded in true epilepsy, where glucose therapy may increase the blood-sugar but has no effect on the fits (Targowla *et al.*) so that the therapeutic test is in these cases a more valuable aid to diagnosis than an estimation of the blood-sugar.

The symptoms of hypoglycaemia often resemble psychoses, such as mania, obsessions, and melancholia; Oppenheimer (1927) cites instances, and Cases 13 and 15 are examples; Sjögren and Tillgren described three cases of confusional violence; one man became unmanageable on several occasions; he threw things about, shouted 'I will murder you', bit, fought, and almost threw himself over the banister; another rushed out of the ward and upset a food-wagon, and a third threatened a fellow patient with a knife. The transitory nature of the unnatural behaviour is an important point in the diagnosis.

Functional nervous disorders such as neurasthenia and hysteria may be closely imitated in hypoglycaemic states.

A young diabetic woman on insulin (No. 41)[3] had attacks of stupor, one of which lasted for three days; the first diagnosis of diabetic coma was revised after an estimation of the blood-sugar, which showed a moderate blood-sugar content. As the attacks were associated with jealousy and family antagonism they were considered to be hysterical, and the patient was sent to a home for nervous disorders, where she was found to have schizophrenic symptoms with

[3] I am indebted to Dr. Helen Boyle for the history of this patient before the hypoglycaemic attack.

a paranoid strain. When an attempt was made to induce her to take up an employment the attacks returned and were thought to be due to a neurotic refusal to face the world; one occurred at 2 p.m. one day when the patient returned late for lunch from a secretarial college: she lay in coma for two hours; the blood-sugar was found to be 0·056 per cent. and an injection of adrenalin immediately restored consciousness. In this case there were three possibilities, hysteria, diabetic coma, and hypoglycaemia.

Intoxication by alcohol and narcotics are almost impossible to distinguish except from the history; one of Cammidge's patients was thought to be a victim of secret drinking although he was really a total abstainer.

If the patient is first seen in convulsions, uraemia, cholaemia, and eclampsia must be considered as well as diabetic coma if it is not known whether the patient has diabetes or not.

In the case of the known *diabetic* the question does not usually arise unless the patient is unconscious or semi-conscious, and the main problem is to decide between diabetic and insulin coma. In the milder stages the patient himself usually knows whether hypoglycaemia is threatening. The following distinctions between the two states may be made: the onset of diabetic coma is gradual and is usually preceded by drowsiness, loss of appetite, and deeper respirations, whereas hypoglycaemic coma may develop in a few minutes.

In diabetic coma the smell of acetone in the breath can generally be appreciated. The skin and tongue are dry in diabetic coma and the patient often dehydrated; in insulin coma the skin is clammy and the tongue moist. The ocular tension is lower in insulin than in diabetic coma. The respiration is deep and slow in diabetic coma, air hunger is present; in insulin coma the respiration is usually shallow; occasionally there may be bradypnoea, as in a case reported by Sigwald (No. 27) where the rate fell to five per minute, but the rhythm was different from the sighing respiration of air hunger; it was violent and explosive with intervals of apnoea lasting for about twelve seconds.

The blood-pressure is often raised in hypoglycaemia and low in diabetic coma, but the difference is not constant, and in hypoglycaemia associated with Addison's disease the tension is of course low.

Examination of the urine, if obtainable, should be diagnostic, but it can mislead. Sugar is usually absent in insulin coma and abundant in diabetic coma, but the presence of sugar does not exclude a diagnosis of hypoglycaemia because in cases of instability, when the blood-sugar varies rapidly, the urine may have been secreted before the onset of hypoglycaemia and may contain sugar; or the renal threshold may be low as in Case 37. On the other hand, diabetic coma may occur with profound acidosis in the absence of glycosuria.

Ketone bodies—acetone and diacetic acid—are always abundant in diabetic coma and are usually absent in hypoglycaemia, but again there are exceptions. It has been pointed out (p. 142) that in advanced diabetes

where there are no glycogen reserves acidosis may be associated with hypoglycaemia. Labbé (1928) recognized that both sugar and ketones may be present.

The nervous signs are not, in general, diagnostic, but stress has been laid on the presence of the Babinski response in insulin coma and its absence in diabetic coma. If present, it is a reliable indication, though it is to be remembered that diabetic coma may be complicated by a pyramidal tract lesion or by uraemia or other intoxication causing a Babinski reflex (Hart, Price-Bond (1929), Hawthorne (1929)). On the other hand, the reflex is not present in all cases of insulin coma, especially in the less severe stages. The writer observed a patient who lay completely unconscious for over two hours but was sufficiently responsive to resent by slight movements the passage of a catheter; no urine was obtainable, but the blood-sugar at the end of the period was 0·056 per cent. The plantar reflexes were tested more than once; the left was definitely flexor, the right 'doubtful'.

The pupils are at about mid-dilatation and the reaction to light is absent or sluggish.

In all doubtful cases an estimation of the blood-sugar is the final appeal; if this is unobtainable it is wise to treat the disease as if it were insulin coma, with glucose or adrenalin; if the diagnosis is correct the patient usually improves within a quarter of an hour; if not, large doses of insulin can be given.

Prevention and Treatment

Spontaneous hypoglycaemia, when the symptoms are slight, can be averted by giving frequent meals, rich in carbohydrate; an orange drink during the night or early in the morning is often sufficient. Seale Harris (1932) considers that a diet relatively poor in carbohydrate and rich in fat, with moderate protein, is more effective, and cites a case when this was so; food is taken every two or three hours and during the night, if necessary. Suprarenal extract by the mouth was given in three cases as an adjuvant (Nielson and Eggleston), but does not appear to have much advantage over diet alone, unless the blood-pressure is low.

When the symptoms persist and increase, the question of *surgical intervention* is to be considered; it has been carried out in nine cases, and resulted in complete relief of symptoms in four. In two of the cases carcinoma of the pancreas was found; one was inoperable (Case 2), but in the other case a small tumour was removed, and a month later the sugar tolerance curve was normal (No. 4). In three cases an adenoma of the pancreas was excised with complete success (Nos. 5 and 6 and a case mentioned by Cushing (1930)).

In four cases (Nos. 9, 10, 11, and 11A) the pancreas appeared normal, and partial pancreatectomy was performed, but without permanent benefit. Surgery offers most hope of success in cases of adenoma of the pancreas, but

these tumours are rare and almost impossible to diagnose; in view of the good results in the three cases mentioned it would seem that exploratory laparotomy is justifiable in cases of severe and increasing spontaneous hypoglycaemia, provided that lesions of the adrenals or pituitary can be excluded. Partial resection of a normal pancreas does not seem to be worth while. Two-thirds of the substance (22·5 grm.) was the largest amount resected (Finney and Finney).

The prevention of the onset of hypoglycaemia in *diabetic patients* treated with insulin needs attention to the following points:

(1) The balance of insulin and diet should be reviewed from time to time and the fasting blood-sugar estimated: when the patient is not under observation he should be warned to reduce the insulin if the urine is persistently sugar-free; slight glycosuria is safe, unless the renal threshold is low.

(2) Care should be taken to reduce the insulin soon enough in recovery from coma and from infections; it is wise to give glucose with insulin in treating diabetic coma, 1 grm. of carbohydrate for each 3 units of insulin (Spriggs).

(3) When exhaustion of glycogen stores is likely, as in states of inanition and starvation or after prolonged exercise, glucose or carbohydrate food should be given liberally with large doses of insulin.

(4) After manifestations of hypoglycaemia, however slight, insulin should be discontinued, reduced, or guarded by abundant carbohydrate until the balance is re-established; the last course is probably the best, as it promotes replenishment of glycogen stores (cf. Case No. 23).

(5) All diabetics on insulin should carry sugar about with them, and eat it at the first warning of symptoms.

(6) Great care must be taken in the administration of insulin to patients suffering from a complication likely to make them abnormally susceptible to insulin intoxication; especially cardiovascular diseases, tuberculosis, and suprarenal deficiency.

In an *actual attack of hypoglycaemia* the indication is to give sugar in any form. If the patient can swallow he should eat sugar, barley sugar, or any sweet food; a sweet drink such as orange juice or lemonade and sugar is absorbed more quickly, but should not be dilute; the taking of any food relieves slight symptoms, and an ounce of sugar or its equivalent is usually ample in severer cases.

When the patient is in coma the intravenous injection of glucose is by far the most certain method of introducing sugar; 10 grm. in 50 to 100 c.c. of sterile saline solution is an adequate dose (Spriggs); Sigwald considers it dangerous to give much fluid, and recommends 10 to 20 c.c. of a 20 or 30 per cent solution.

Subcutaneous glucose in isotonic solution may be given; rectal glucose, 7½ per cent., is often administered, but Harris (1932) considers it futile and cites evidence to show that it is not absorbed; in Case No. 35 glucose per

rectum hardly raised the blood-sugar, but in Case No. 37 it was the only treatment used, and recovery ensued, though slowly. If it is impracticable to give intravenous glucose, it is probably best to introduce a strong solution directly into the stomach by means of an oesophageal tube.

Sometimes death occurs in spite of doses of glucose, which should be amply sufficient to restore the blood-sugar; for example, a child aged 8 received 107 gr. of glucose, the greater part intravenously, but the blood-sugar fell during treatment from 0·093 to 0·052 per cent. (Heimann-Trosien and Hirsch-Kauffmann). In some cases the blood-sugar can only be raised temporarily, and this occurs especially in spontaneous cases with increased secretion of insulin, but it may happen in diabetics, especially if there are complications; for example, in Rosendahl's tuberculous Case No. 29, 55 grm. of glucose caused the sugar to rise from 0·042 to 0·060 per cent., but it fell shortly to 0·048 per cent., and the patient died. A case described by Root (No 42) illustrates the difficulties encountered when there is infection.

A woman of 51 had a gangrenous toe and pyrexia (101° F.–102° F.). The fasting blood-sugar, which had been 0·40 per cent. on admission, fell to about 0·20 per cent., and the urine became sugar-free on 60 units of insulin a day; an attempt was made to bring the blood-sugar to normal, as the pyrexia persisted after amputation of the toe; and a dose of 80 units three times a day (240 units in twenty-four hours) was reached by rapid increase; the blood-sugar suddenly fell to 0·015 per cent. The leg had been amputated three days before, and the temperature was lower, so that recovery from infection may have made the patient less resistant to large doses of insulin.

Uraemia supervened, as it often does in diabetic coma, and probably contributed to the fatal result. Two intravenous injections of glucose were given, after each of which consciousness returned, but the patient died in a third relapse before glucose could be administered. The danger of giving large doses of insulin when the blood-sugar is approaching normal is apparent here.

Another disturbing occurrence is that several patients have died although the blood-sugar was restored to normal or above; this was so in the first case of death from insulin intoxication reported from Scandinavia (Dahl).

(*Case No. 43.*) A woman of 52 was admitted in the early stages of diabetic coma with a blood-sugar of 0·385 per cent., the urine was loaded with sugar and acetone and contained albumin; she recovered well with moderate doses of insulin, and was sugar-free on the following day with a blood-sugar of 0·144 per cent., though acetone was present until the ninth day of treatment. Glycosuria occurred intermittently during the week, and the insulin had been increased from 15 units in three doses on the fourth day to 35 units on the eighth (10.15.10). On the morning of her fatal attack the blood-sugar was 0·165 and the urine free from sugar and acetone. She had 10 units of insulin early and 15 before her midday meal, but did not eat her bread; three hours later she was in deep coma with a blood-sugar of 0·025 per cent.; seven hours after the onset of coma the blood-sugar had been raised to 0·380 per cent. after injection of adrenalin and sugar, but she died without recovering consciousness nineteen hours after the onset, her blood-sugar being 0·089 per cent. two hours before death.

In Chabanier's case (No. 38) the blood-sugar was raised to 0·26 per cent., and yet death occurred. In cases such as these it is probably not the low blood-sugar that brings about the fatal result (cf. p. 121).

The injection of adrenalin, 15 minims of a 1 in 1,000 solution, is a rapid method of treatment, provided that the glycogen stores are not exhausted. Pituitrin 1 c.c. is equally effective.

Caffeine has been found beneficial. Popper and Jaboda injected 1·4 grm. of caffeine sodium benzoate.

The injection of calcium chloride is said to be of use in the treatment of convulsions, and the administration of calcium lactate in their prevention.

Danger of accidents. Should insulin patients drive motor-cars? is a question that has been raised recently in Scandinavia (*Lancet*, 1932). A Danish lorry driver, aged 25, having taken his insulin at 8 a.m., was called out before breakfast; he took some food with him, but partly lost consciousness while beginning to eat it, and his lorry charged a stationary vehicle. Such accidents are not common but are always possible, especially with patients who need large doses of insulin or whose blood-sugar equilibrium is unstable. Professor Holst and Dr. Müller, who published a memorandum in the report of the Norwegian Medico-legal Commission, recommend that insulin patients should not be allowed to drive taxis or motor omnibuses, and that permission to drive a car should be dependent on a medical certificate that the insulin balance is regulated and steady, and is understood by the driver.

Other occupations may be dangerous either for the patient or to others; Sonne reports the case of a man in the railway service who on many occasions was found 'wandering senseless about the railway grounds' in attacks of hypoglycaemia.

Although diabetics on insulin are able to carry out almost any work or profession, they are not suitable for strenuous occupations where a momentary loss of control is fatal—for instance, that of engine-driver, air pilot, or racing motorist.

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UVEO-PAROTID TUBERCULOSIS[1]

(FEBRIS UVEO-PAROTIDEA OF HEERFORDT)

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(From the General Infirmary, Leeds)

With Plates 16–18

Introduction

In 1909 Heerfordt (21) described a clinical syndrome characterized by inflammatory lesions of the uveal tract, and enlargement of the parotid glands, both running a chronic and usually febrile course, and frequently complicated by paralysis of the cerebrospinal nerves, especially the facial. In 1923 Berg (4) reviewed forty cases, and since then about twenty more have been recorded; most of the cases come from the Scandinavian countries and Germany, very few having been reported in England and America. The case reports have usually appeared in ophthalmological journals, and in consequence the condition has not received widespread recognition, which, in our opinion, accounts to some extent for the infrequency of reports in the English-speaking countries.

The majority of cases appear under the title of 'febris uveo-parotidea (Heerfordt)' or simply 'uveo-parotitis', others as 'uveo-parotitic paralysis (Macbride)', but in view of what we believe to be the invariable pathology of the condition 'uveo-parotid tuberculosis' is suggested as a more correct designation.

Clinical Manifestations

We have analysed forty-seven cases including our own. The majority occur in the second and third decades, 62 per cent. being under the age of 30, with extremes of 7 and 59. There were 18 males and 28 females (one sex unknown):

Decades.	Males.	Females.	Total.
0–10	2	0	2
11–20	9	7	16
21–30	2	12	14
31–40	3	3	6
41–50	1	3	4
51–60	1	3	4

Prodromata. Prodromal symptoms were noted in twenty cases, lasting

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from a few days to three months (Hamburger and Schaffer (19)). Malaise, lassitude, and drowsiness occurred in ten, and gastro-intestinal symptoms, including nausea, anorexia, diarrhoea, and vomiting, in a further seven; less common were skin eruptions, especially erythema nodosum, pyrexia, joint-pains, paraesthesiae, ill-defined cerebral symptoms, cough, amenorrhoea, night sweats, and puffiness of the eyes.

Parotitis. There was bilateral, though not always symmetrical, enlargement of the parotid glands in forty-five cases and unilateral enlargement in two (Critchley and Phillips (10), Müller (34)). Parotid enlargement was the first physical sign in sixteen out of thirty-three in which there was adequate information, and in three further cases parotid enlargement and uveitis were simultaneous. The swelling usually commences in the pre-auricular portion of the gland, to which it may be confined throughout, and frequently one gland is affected before the other. The swelling, generally of moderate degree, is firm, nodular, and almost invariably painless, although occasionally the glands are tender on pressure. The glands, which never suppurate, slowly subside after an interval varying from two weeks (our case) to three years (Merrill and Oaks (32)). There is no attachment to the overlying skin, which is normal, and mastication is usually neither painful nor appreciably impeded; recurrence is almost unknown, but there may be permanent induration. Enlargement of the submaxillary glands occurred in five cases, and of the sublingual in one, but never to a marked degree and the duration was usually shorter than that of the parotitis. Enlargement of the cervical lymph nodes has been noted in only three cases. In nine there was swelling of both lachrymal glands and in most of them a diagnosis either of Mikulicz's disease complicated by inflammatory lesions in the eyes, or of the 'Mikulicz-Heerfordt' syndrome, was made. It is certain that many more cases have been recorded under these titles, e.g. those of Heine (quoted by Cavara (7)). Generalized adenopathy has been noted (Lehmann (26)) as has splenomegaly (Hamburger and Schaffer (19)).

Ocular manifestations. Bilateral uveitis occurs in every case and was the first symptom in twelve out of thirty-three. Of its numerous manifestations, irido-cyclitis is the most constant, being described in forty-two cases. The onset may be sudden or gradual, is sometimes accompanied by pain, and usually develops on one side before the other. There is a great tendency to the development of posterior synechiae, and, although the ocular manifestations usually improve, permanent pupillary changes, fixity, irregularity of outline and inequality, are common (eighteen cases). Iris nodules were noted in a third of the cases, and in some of these a definite diagnosis of tuberculosis was made. Vitreous opacities occur in half the cases, and it is common for the patient to be left with permanent impairment of visual acuity sometimes resulting in total blindness; Bang (2) collected five such cases in 1918. Less common manifestations of the uveitis are vitreous haemorrhages, corneal herpes and opacities, keratitis, optic neuritis, neuroretinitis, choroidoretinitis, glaucoma, aqueous turbidity, and cataract. Photophobia

is not infrequent (nine cases). In a single instance a central scotoma was noted (Souter (47)), in three there was ptosis (Critchley and Phillips (10), Souter (47), and our case) and in two there was lachrymation (Critchley and Phillips (10) and Ramsay (38)). Several have also shown conjunctivitis, probably the result of rubbing.

Unlike the parotid lesion, the uveitis not infrequently relapses, sometimes more than once, and this may be associated with general disturbances. The duration of the ocular signs is usually longer than those of the parotid and in one case (Schou (46)) there was a relapse after two years. Lehmann (27) thought that the eye signs were worse and of longer duration in cases where glands other than the parotids were affected. Schall (44) goes so far as to say that there is a uveitis typical of uveo-parotid fever with the following characteristics. The exudates, which are persistent, are large, pigmented, and 'bacon-like' and present a star-shaped appearance with the slit-lamp similar to Koeppe's description of tuberculous iritis. The anterior chamber exudates are slight and usually disappear in a few weeks.

Facial palsy. Facial palsy has been noted in twenty cases out of thirty-six; it was bilateral in eight and unilateral in twelve, of which nine were right- and one left-sided (in two side not stated). The facial palsy, which is of sudden onset, usually follows the parotitis, the interval varying from a few days to six months (Macbride (28)), but in two cases (Feiling and Viner (15) and Lehmann (26)) it was the first symptom, and in two others it preceded the parotitis by as much as four weeks (Lehmann (26) and Leeksma (25)). In four cases (Heerfordt (21), McCulloch (29), Thomsen (48), and Uhthoff (50)) it occurred simultaneously with the parotitis.

The duration of the palsy varies considerably, but is usually a few weeks, the longest being one year (Lehmann (26)). In Altland's (1) and Reith's (40) cases it developed while the parotitis was subsiding. In four (McCulloch (29), Macbride (28), Ramsay (38), and Reith (40)) it appeared after all signs of parotitis had subsided, the interval varying from one week to six months; in Lehmann's two cases (26) the facial palsy improved as the parotitis increased. In one case only, that described independently by Daireaux (12) and Péchin (37), was taste impaired; in Lehmann's third case (26) the facial muscles showed partial reaction of degeneration. The lower part of the face is often more affected than the upper, and it may be the last to improve.

Pyrexia. In spite of the fact that the condition is described as 'febris uveo-parotidea' we find that only twenty-three cases have been febrile at some stage of the illness, justifying the suggestion of Schall (44) that pyrexia is not an essential part of the syndrome. In three instances pyrexia was limited to a slight rise of temperature during the prodromal period. The fever is never maintained, is always very mild (limited to an evening rise), and has rarely exceeded 101° F., though Hamburger and Schaffer's case reached 103°. In our own case there was persistent tachycardia out of proportion to the temperature.

Signs of nervous disease. Excluding facial palsy we have been able to find surprisingly few instances of involvement of the nervous system, viz.: dysphagia (Heerfordt (21), Macbride (28), Ramsay (38), Mackay (30), Critchley and Phillips (10), and Cavara (7)); paralysis of the soft palate and intercostal neuralgia (Ramsay (38)); paralysis of the vocal cords and paraesthesiae (Heerfordt (21)); impairment and ultimate loss of ankle- and knee-jerks (Feiling and Viner (15)); paraesthesiae of arms and legs with some weakness of the legs and a slight left-sided deafness of doubtful origin (Macbride (28)); ptosis, wasting of hand muscles, and loss of vibration sense in the legs (Critchley and Phillips (10)); slight ptosis, central scotoma, and absence of knee-jerks (Souter (47)), and in our own case signs and symptoms of mild polyneuritis.

Other manifestations. Skin eruptions were noted in eight cases at some stage of the disease: erythema nodosum (Brewerton (5), Ramsay (38), Merrill and Oaks (32)); erythema of arms and face (Brewerton (5)), of legs (Leeksma (25), Souter (47), and Feiling and Viner (15)) and over both body and extremities (Altland (1)). In Parker's case (36) a papular rash on the forearms followed a prodromal erythema.

Dry mouth was noted in eight cases, and polyuria in three (Heerfordt (21), Merrill and Oaks (32), and our case). The urine was always found to be normal, and we think the polyuria is probably due to excessive fluid intake consequent on the dry mouth. Joint pains occurred in three cases (Critchley and Phillips (10), Merrill and Oaks (32), and Souter (47)).

Laboratory Investigations

Examination of the blood was carried out in sixteen cases, of which six showed a moderate polymorph leucocytosis, three an eosinophilia (Kaitz 8 per cent. (23), Thomsen 20 per cent. (48)), and two a leucopenia (Lehmann (26)). Secondary anaemia was present in two (Jackson (22) and Critchley and Phillips (10)), and the remaining three gave normal figures. In our own case, although the total leucocyte count was normal, there was an appreciable shift to the left of the Arneth count. Blood culture was performed with negative results in seven cases. The cerebrospinal fluid was normal in five cases, and in two the only abnormality was an increase in the cells, one with eight (Macbride (28)), the other with fifteen (Feiling and Viner (15)) lymphocytes per c.mm. The Wassermann reaction was carried out in thirty-one cases with negative results in twenty-seven; three were positive (Mohr (33), Vasek (51), and Gjessing (17)), and in another in which the first test was doubtful the reaction was found to be negative after a dose of N.A.B. (Berg (4)). Bacteriological examination of the conjunctiva and of the parotid secretions showed only the normal flora, and pus cells were not found.

Case Report

B. H., a female aged 28, had rather indifferent health all her life and as a child suffered from chicken-pox, measles, and diphtheria (twice). In 1927 there was amenorrhoea for twenty weeks and for some years she suffered from dyspnoea on exertion. Early in 1931 she had 'influenza and bronchitis' which were followed by 'rheumatic' pains. There was no family history of tuberculosis.

In August 1931 she developed acute painful irido-cyclitis of the right eye, and a week later bilateral painless enlargement of both parotids. Five weeks later (sixth week) iritis developed in the left eye. The parotid swelling slowly disappeared after two weeks. Towards the end of October she completely lost her voice, and about the same time she noticed tremor of the hands with some clumsiness of gait. She was admitted to the Leeds General Infirmary under Mr. S. D. Lodge on November 20, and was then complaining of 'pins and needles' in the feet of four days' duration. Throughout the illness the chief symptoms present were progressive weakness and lassitude, amenorrhoea, excessive thirst with polyuria, some urgency of micturition, and, for nine weeks, complete distaste for sweet foods. She was constipated, which was unusual for her, and had lost about one and a half stones in weight.

Examination. A pale, slightly built young woman, intelligent, co-operative, and normally orientated in time and space; no speech defect. Examination by Mr. J. Benson, Resident Ophthalmic Officer, showed visual acuity 6/36 (R.) and 6/18 (L.); visual fields and eye movements full, no diplopia or nystagmus. Pupils unequal and fixed both to light and on accommodation. Both eyes showed almost total posterior synechiae with keratitis punctata in the right. On slit-lamp examination both anterior lens-capsules showed pigmentation. Fundi not seen owing to haziness of the vitreous; intra-ocular tension normal; corneal reflexes sluggish. There was slight bilateral ptosis and the face was smoothed out and expressionless, but there was no asymmetry or weakness; taste and smell not impaired. The tongue was protruded in the middle line and showed complete absence of furring with a small central area of smoothness. Arms slightly hypotonic and assumed the choreic position; there was slight ataxia of sensory type; no wasting or fibrillation, but muscular power diminished. Mild bilateral foot-drop, the legs being hypotonic and weak. Tendon-jerks brisk and equal on the two sides; upper abdominal reflexes sluggish, lower absent; plantar responses flexor. Pain, temperature, light touch, vibration, and postural senses not impaired. Gait markedly ataxic with unsteadiness on standing. Calves rather tender on deep pressure. No abnormal signs in heart or lungs; a few patches of pityriasis versicolor under the breasts. Blood-pressure 120/78 mm. Hg. Salivary glands, lymph nodes, and spleen not enlarged.

Special investigations. There was a complete achlorhydria with excess of mucus in the stomach. Blood count: red cells 4,250,000 per c.mm.; haemoglobin 70 per cent.; colour index 0·82; leucocytes 5,800. Arneth count: 44, 37, 17, 2, 0 (index 1.77, i.e. a marked shift to the left). Cerebrospinal fluid: 2 lymphocytes per c.mm.; protein 0·03 per cent.; Pandy test negative; Lange test negative; sugar 0·075 per cent.; Wassermann reaction negative. Blood Wassermann reaction negative. Von Pirquet test negative. The sputum contained no tubercle bacilli (three examinations) and

guinea-pig inoculation was negative. X-ray of the chest showed no abnormality. Blood culture negative. There was no evidence of sinus infection, but on admission there was simple chronic laryngitis; the gums were congested, with purulent discharge as well as X-ray evidence of pyorrhoea alveolaris. The urine was sterile. Sialography by Mr. L. N. Pyrah showed no abnormality of the parotid ducts.

During the next three weeks there was irregular pyrexia up to 100° F. with persistent tachycardia ranging from 96 to 110. The hoarseness disappeared, as did the tenderness of the calves, but on December 12 she complained of a sore throat and the temperature rose to 101° F.; the tonsils and fauces appeared normal. This attack subsided in three or four days and the temperature became normal although the pulse remained rapid. On December 17 she vomited and said she did not feel well; on the following day respiration became embarrassed and, after increasing cyanosis and dyspnoea, she died in the early hours of December 20.

Autopsy. The post-mortem examination was performed thirty hours after death by Professor M. J. Stewart.

The body was that of a fairly well-nourished young woman. The left *tonsil* contained a quantity of epidermic débris and the right was slightly inflamed; in both the crypts were enlarged. *Larynx*, *trachea*, and *bronchi* contained a quantity of thick, discoloured muco-pus, and the mucosa of these passages was much congested. *Tracheo-bronchial glands* moderately anthracotic and somewhat congested, with no naked eye evidence of tuberculosis on section. *Parotid glands* very small and densely fibrosed. *Submaxillary glands* appeared normal; *cervical lymph nodes* not enlarged and not obviously tuberculous; *pleurae* normal. Both *lungs* were riddled with excessively fine miliary tubercles showing up prominently on a congested background. They were all approximately the same size, and there was no evidence of an older lesion in the lungs. The *pericardium* showed generalized very acute miliary tuberculosis of the visceral layer with almost nothing showing on the parietal layer; the tubercles were seen most easily on the surface of the ventricles and were very close set. The *myocardium* was the seat of massive tuberculosis. On cross-section (Fig. 1) the right ventricle was almost completely replaced by lighter coloured tuberculous tissue, but in the left only the outer half of the wall was involved. The affected areas were firm and white and no caseation could be seen. The right ventricle showed considerable uniform dilatation without aneurysmal bulging. The valves appeared normal and the coronary arteries were healthy. The aorta showed a few scattered areas of fatty streaking. *Liver* distinctly enlarged, weighing 63 oz.; on section pale and somewhat fatty looking, with intense toxic changes and almost complete loss of normal lobulation. No miliary tubercles could be seen on the cut surface, but they were present on the portion of the organ covered by peritoneum. The *spleen* weighed 9 oz.: the pulp was much softened and not obviously tuberculous on section. *Suprarenals* soft and cortical lipoid reduced. The *kidneys* were considerably enlarged, the capsules being adherent and the surface granular. On section, the outer surface was studded with closely set miliary tubercles. At several points in the cortex there were whitish areas of larger size almost certainly tuberculous. There was well-marked tuberculosis of the *peritoneum*. Miliary tubercles were seen on the serous surface of the *uterus*, which was otherwise normal apart from the presence of a small semi-pedunculated polypus in the middle of the posterior wall of the body. The *large intestine* showed slight melanosis involving the caecum and ascending colon and fading

rapidly away in the transverse colon; the appendix was retrocaecal and bound down by old adhesions, the lumen of the distal half-inch being obliterated. The *mesenteric glands* were enlarged from the presence of old tuberculous disease with much caseation and calcification. The following organs appeared normal to the naked eye: oesophagus, duodenum, small intestine, thyroid, ovaries and tubes, brain, spinal cord, and membranes.

Histological examination. Right parotid: this is much reduced in size and contains only a small amount of glandular substance; it is traversed by broad bands of rather hyaline fibrous tissue dividing the gland into lobules (Fig. 5). The larger ducts lie in the middle of these grossly thickened septa, and although many of them appear quite normal others are surrounded by a zone of tuberculous granulation tissue containing follicularly arranged endothelioid cells, lymphocytes, and scanty giant cells (Fig. 7). The surviving parenchyma is the seat of extensive recent miliary tuberculosis without caseation, and only an occasional giant cell, but older foci with well-formed giant cells are sometimes seen (Fig. 8). Lehmann (27) suggested that the nodularity of the enlarged parotids was due to involvement of the parotid lymph nodes, and it is interesting to find that the two lymph nodes present in this parotid were involved neither in the tuberculosis nor in the fibrosis. They are seen, rather darkly stained, at the lower end of Fig. 5, and their relatively large size indicates well the degree of cirrhosis of the parotid gland. *Left parotid*: here the fibrosis is less marked, although no more gland tissue survives than on the right side (Fig. 6); the miliary tuberculosis is even more extensive. *Submaxillary glands*: these show a miliary tuberculosis of similar type without any appreciable caseation. The ducts are normal and there is no fibrosis. *Pancreas*: there is considerable autolytic change and no evidence of tuberculosis. *Liver*: numerous miliary tubercles are present of approximately the same size and appearance; these contain many endothelioid cells and lymphocytes, but no giant cells, and show very little necrosis; they have all crisp rounded margins and are very well demarcated from the liver parenchyma; the liver cells show considerable cloudy swelling and the Kupffer cells are rather prominent. *Spleen*: the pulp is congested and the sinuses are well marked; there is no evidence of tuberculosis. *Kidney*: extensively affected by tuberculosis, mainly of miliary type, and presenting the same histological features as in the liver, but larger and older foci are also present. These often have giant cells and, with van Gieson or Mallory's connective tissue stains, collagenous fibres can be demonstrated at their margins; again no caseation is present. The miliary tubercles are almost confluent in the cortex, and are fairly numerous in the medulla; the kidney otherwise shows marked congestion and some degenerative tubular changes. *Lungs*: numerous miliary tubercles are present, similar to those in other organs, but there is no evidence of older tuberculosis in the sections examined; there is considerable congestion and oedema, especially in the bases. *Uterus*: there is an extensive miliary tuberculosis, most marked in the serosa and endometrium, but with scattered tubercles also throughout the myometrium. The *brain* and *membranes*, the *spinal cord*, and the main trunks of the median and sciatic *nerves* show no histological abnormality. *Heart*: the pericardium is dotted with miliary tubercles of the same size and appearance as those occurring elsewhere. The myocardium is largely replaced by tuberculous granulation tissue containing endothelioid cells, lymphocytes, and numerous giant cells, with a varying amount of fibrous tissue (Figs. 3 and 4). In places where the cellular infiltration is marked, only fine collagenous fibres can be demonstrated by Mallory's connective tissue stain; elsewhere the surviving

bands of heart muscle are widely separated by fairly dense fibrous tissue, which, however, contains abundant endothelioid cells and giant cells. Nowhere is there any necrosis, and the muscle fibres appear quite normal except in the very cellular areas where they are separated by oedema. The process would appear to be extending along the fibrous septa and accompanying the blood-vessels, but the tuberculous arteritis which was such a prominent feature in the myocardium of Souter's case (Thomson (49)) is quite lacking. Some of the larger branches of the coronary arteries have a zone of tubercles in or surrounding their adventitia, but this is probably evidence of the lymphatic spread only. Typical tubercle follicles are present in the margins of the advancing process, elsewhere the lesion takes the form of the granulomatous type above described. The histological picture is similar in all the sections studied, the only variation being in the degree of fibrosis accompanying the cellular infiltration. The coronary vessels are normal.

Staining for the tubercle bacillus by Ziehl-Neelsen's method gave repeatedly negative results, but in view of the non-caseating nature of the tuberculosis, and the unusually fibroblastic response on the part of the patient, this is not altogether unexpected. The material was unfortunately not injected into guinea-pigs, but the histological characters are so typical that we have no doubt as to their tuberculous nature, in spite of the unusual distribution of the lesions. Scanty tubercle bacilli were found by one of us (Thomson (49)) in the heart of Souter's case after grinding up a portion and digesting it with sodium hydroxide, but a similar procedure in the present case gave negative results.

Additional Cases

By the kindness of Dr. H. Batty Shaw, Dr. Macdonald Critchley, and Dr. F. R. Ferguson, we are able to refer to two further cases, not typical examples of the syndrome, and not included in the above analysis.

The first of these, a woman aged 55, was seen by Dr. Batty Shaw in January 1928, when she complained of cough and loss of weight. Twenty years before she had complained of eye trouble, which had been diagnosed as irido-cyclitis, and which had relapsed in 1926, when a diagnosis of irido-cyclitis was again made by Dr. Griffith Thomas of Swansea. In addition to photophobia she now complained of dryness of the mouth which has persisted. The recurrence of 1926 was also associated with painless swellings in front of both ears, but there was no pyrexia. At the time of examination in 1928 the only abnormality discovered was xerostomia. In September 1930, she was seen by Dr. Macdonald Critchley; there was no family history of tuberculosis; on examination the pupils were unequal and inactive, the left cornea was hazy, the iris muddy, and the pupil irregular, the disk not being seen. The right optic disk was normal. There was a flat swelling, painless, hard, and smooth, in front of the right ear; the left parotid showed diffuse, brawny, hard swelling. The other salivary glands, the lachrymal glands, and the lymph nodes were normal. The tongue was red, shiny, and dry, and there was marked xerostomia. Examination of the nervous system showed no abnormality, with the exception of bilateral ptosis; blood pressure normal. X-ray examination of the chest showed no abnormality; blood Wassermann reaction negative; blood count normal; fractional test meal showed hypochlorhydria.

The second case, a girl aged 17, was seen by Dr. F. R. Ferguson in February 1932. On January 1st she had noticed that the face was drawn over to the right side, and as there was slight swelling a tooth was extracted; after five weeks the face 'went straight', and she developed neuralgic pain in the right side of the face with some earache; after six weeks both sides of the face were paralysed, and she was unable to close her eyes. On examination (February 29) there was bilateral facial palsy: the pupils were dilated and fixed, and an ophthalmic surgeon diagnosed bilateral irido-cyclitis. There was no pain or swelling of the parotids, and no other abnormal signs; the Wassermann reaction was negative. At a subsequent examination the eye condition had improved, the pupils were less widely dilated, and the facial palsy was less marked. At no time had there been any pyrexia, and there was no definite history of parotid swelling. In July the patient wrote to say that she was feeling very well, and that the eye condition was improving every day.

The first of these cases is typical in regard to the irido-cyclitis and bilateral parotitis, but unusual on account of the age of the patient, the very long history, and the persistent parotid enlargement. The second showed bilateral irido-cyclitis with facial diplegia, but without parotitis; it cannot, therefore, be regarded as a case of Heerfordt's syndrome, although it is quite conceivable that the parotitis may have been so slight as to escape the patient's notice.

We do not consider the case recorded by Rogers, Bodman, and Coombs (42), and included in the analysis of both Parker (36) and Merrill and Oaks (32), to be an example of this condition, on account of the absence of uveitis. The two cases recently recorded by Ortega (35), however, are probably examples of Heerfordt's syndrome, although they are reported as 'iritis of parotid origin'. Others which, for various reasons, are not included in the preceding analysis are those of Coppez (9), Edmund (quoted by Lehmann (26)), Fleischer and Ohno (quoted by Berg (4)), and Schneider (45).

Aetiology

In his orginal paper Heerfordt described three cases, and referred to others with similar symptoms which he had found in the literature, namely that described first by Daireaux (12), and later by Péchin (37), and that of Collomb (8); these latter were ascribed to a complication of mumps, and Heerfordt was of the opinion that his cases had a similar aetiology. In 1914 Schou (46) published a case of Heerfordt's syndrome in which the uveitis preceded the parotitis, and the discovery of a nodule in the iris similar to a tuberculous nodule led to the diagnosis of tuberculous iritis. Two years later Kirstine Lehmann (26) reported three cases one of whom (Case 2) was suffering from pulmonary tuberculosis and had a positive sputum, and another (Case 1) had a strong family history of tuberculosis and showed, in the iris, nodules similar to those of tuberculosis. Her third case was not obviously tuberculous and died some time after, the post-mortem findings being those of pernicious anaemia, which in Lehmann's opinion had nothing to do with the uveo-parotid lesions. She also referred to Uhthoff's case (50), published in 1909 and an undoubted example of the syndrome, in which a diagnosis of tuberculous meningitis with tuberculous irido-choroiditis with

iris nodules had been made. In this patient there was clinical evidence of pulmonary tuberculosis, a positive von Pirquet reaction, and improvement under tuberculin treatment. Lehmann also followed up Heerfordt's original cases. Case 1 showed a relapsing irido-cyclitis with extensive posterior synechiae; after some time the intra-ocular tension increased, for which a bilateral iridectomy was performed. The resected portions of iris contained nodules which histologically showed a typical tuberculous lesion, with endothelial cells, lymphocytes, and giant cells; caseation was absent and no tubercle bacilli were found. At a later date cataract developed, and during the next few years various operations were performed on the eyes. After ten years vision in both eyes was markedly impaired, though the general health was very good. Heerfordt's second case developed a vitreous haemorrhage two and a half years after the onset, and at this time he had repeated attacks of haematemesis; he died as a result of an accident, but there was no autopsy. Heerfordt's third case was quite well nine years later, but had permanent posterior synechiae and pupillary changes. Lehmann also followed up Schou's case (46) in which the irido-cyclitis had relapsed after two years, when there were iris nodules, posterior synechiae, and bilateral cataract.

In the second part of her paper Lehmann (27) concluded that Heerfordt had described a well-characterized condition and not a complication of mumps, giving as her reasons the long prodromal period, the indolence of the parotid swelling, which may last as long as two years, the fact that the facial palsy may precede the parotitis by as much as four weeks, and the absence of orchitis. In addition a history of contact with mumps is lacking, and these cases do not infect other people with mumps; and finally uveitis complicating mumps is generally unilateral. She concluded that uveo-parotid fever is due neither to mumps nor to syphilis, but may be due to an atypical form of tuberculosis, although this is not definitely established.

Leeksma (25) in 1916 described a case in a woman aged 28, and in view of the negative Wassermann and von Pirquet reactions, and the fact that he had had three cases of mumps in the patient's vicinity at the time, decided that it was a case of atypical mumps. But the patient had prodromal features of night sweats and giddiness for four months, and the facial palsy on the right side, which preceded the right parotid swelling by one month, had disappeared two weeks before the latter developed. In the same year Kuhlefeld (24) described a typical case in a woman aged 21, in whom there was a strong family history of tuberculosis, and who had had mumps as a child.

Bang (2) recorded two cases in 1918, and considered that the association of bilateral parotitis and lachrymal enlargement is found only in Mikulicz's disease, which he thought to be a form of pseudo-leukaemia. He suggested than the iris nodules might be lymphomatous infiltrations, and in spite of the biopsy findings of endothelial cells and giant cells in these nodules, advised classifying uveo-parotid fever in the pseudo-leukaemia group rather

than ascribing it to tuberculosis. Later, however, one of his patients died, and *post mortem* showed miliary tuberculosis.

In 1919 Thomsen (48) reported the case of a slightly built girl aged 18, with a history of amenorrhoea for three months; she developed bilateral parotitis and irido-cyclitis said to be typically tuberculous; the von Pirquet reaction was negative, but later the subcutaneous injection of tuberculin was followed by a notable focal and general reaction. The patient was given a course of therapeutic tuberculin (16 injections), with rapid improvement of the iritis, and of the general health, and return of the menses. In commenting on this case Thomsen was convinced that it was due to a special form of tuberculosis and not to mumps or syphilis.

In the same year Reith (40) noted the case of a girl aged twelve and a half who developed bilateral parotitis, said to be due to mumps then epidemic in the neighbourhood. The parotids, however, were still swollen after an interval of three months, and later she developed an irido-cyclitis with nodules diagnosed as tuberculous. X-ray examination of the chest revealed a marked enlargement of the bronchial glands, and after eleven months the iris was said by Professor Weill of Strasburg to be typically tuberculous. Reith refers to several examples of irido-cyclitis complicating mumps, all of which, however, were reported before 1909. Feiling (14) in his critical review was unable to find a single reference to iritis complicating mumps. Reith thought that mumps cannot with certainty be excluded as the cause of uveo-parotitis, although most of the cases examined by modern methods point to a tuberculous aetiology, and considered that syphilis or tuberculosis is the cause of the parotitis. Bentzen (3) in 1918 believed his case to be tuberculous in spite of the absence of iris nodules, and he used tuberculin therapeutically.

In the cases of Mohr (33), Gjessing (Case 1 (17)), and Vasek (51), there was serological evidence of syphilis, but treatment with mercury and iodides had no effect in Vasek's case, and while there was improvement of the uveitis after a course of antisyphilitic treatment in Mohr's case, there was no change in the parotitis. Gjessing thought his case to be due to syphilis, but two years later he published a paper on 'Tuberculosis as the aetiology of the so-called Febris uveo-parotidea (Heerfordt)' (18), describing a second case with a typical 'habitus phthisicus', and in whom the subcutaneous injection of 1 mg. of old tuberculin was followed by a severe focal reaction in the eyes. He concluded by agreeing with Lehmann that mumps is not the cause, and that it is probably a manifestation of tuberculosis.

Müller (34) in 1920 supported the tuberculous theory in recording the case of a boy who showed nodules in the iris morphologically resembling those of tuberculosis; a biopsy from the parotid gland gave the histological picture of tuberculosis of an endothelioid type; tubercle bacilli, however, were not found, and injection of the material into a guinea-pig gave negative results.

Schall's case (44) was treated by tuberculin, and after nine months vision was normal in both eyes; he thought that a distinction should be made

between the acute uveitis occurring as a complication of mumps, and the more chronic uveitis in older patients with painless parotid swelling which are examples of Heerfordt's syndrome. In his opinion the name should be altered to 'Uveo-parotidea subchronica tuberculosa', as tuberculosis is the cause, while fever is an inconstant finding.

In 1923 Berg (4) reviewed forty cases from the literature, including one of his own, and agreed that tuberculosis was the most likely cause of the condition. A year later Altland (1) could find no evidence of tuberculosis in his case, and was inclined to believe that this very rare disease was a definite symptom complex due to an unknown agent. Reimers (39) in 1926 reported the case of a boy aged fourteen in whom there was X-ray evidence of massive tracheobronchial gland enlargement; the von Pirquet test gave a delayed positive reaction, and treatment by tuberculin was followed by rapid diminution of both parotitis and uveitis. A biopsy was performed on one of the parotids and microscopic examination showed much fibrosis with endothelioid tubercles surrounded by lymphocytic infiltration, but without giant cells or caseation. Two weeks later, when the parotid swelling had quite disappeared, another biopsy was done and the material injected into two guinea-pigs, which up to the time of the report had given negative results. Reimers concluded that all the evidence pointed to tuberculosis as the cause in his case and, after referring to authors whose findings were similar to his own, suggested that tuberculosis of a cirrhotic and benign type was the cause of uveo-parotid fever.

Weve, however, was one of the few later continental writers to express a contrary opinion. He described a typical case in 1916 (52) in which he claimed to have excluded tuberculosis and thought that it was a special form of mumps. More recently he encountered another example of the condition in the brother of the case he had studied some years before. The symptoms and signs were similar in the two cases, both falling ill at the age of seven. Although a biopsy from the parotid gave the histological picture of endothelioid tuberculosis, he did not consider that his cases were due to tuberculosis in view of the lack of tuberculous family history, the negative clinical examination, the repeatedly negative von Pirquet tests, the absence of reaction, focal or general, after the subcutaneous injection of 20 mg. of old tuberculin and, lastly, the failure of animal inoculation tests. He injected portions of the parotid glands into the anterior chamber of the eye in a rabbit and intraperitoneally into guinea-pigs, none of which developed tuberculosis. While he admits that one can be quite certain of the tuberculous aetiology in a few instances, Weve thinks that if more cases are similarly investigated by animal inoculation, and give negative results, it will become more certain that we are dealing not with tuberculosis, but with an unknown aetiological agent, which from the tuberculous-like histological findings can be termed 'para-tuberculosis'.

Two years later Cavara (7) recorded the case of a woman aged 55, who presented a typical picture, except that the lachrymal glands were also affected.

There was no family history of tuberculosis, no nodules were seen in the iris, and the von Pirquet test was negative, but the patient had had a cough for years, there were clinical signs of tuberculosis in the right lung, X-rays demonstrated enlarged hilar glands and a cavitating lesion in the right lung, and the subcutaneous injection of tuberculin was followed by a focal and general reaction with an increase in the temperature. Biopsies were performed on the lachrymal glands and the left parotid. Portions of the former were implanted into the anterior chamber of the eyes of three rabbits, in two of which secondary infection occurred with loss of the eyes, while in the third the tissue was absorbed after two months with no resulting pathological change. Further pieces of lachrymal gland were injected into three guinea-pigs with negative results in two, but the third showed progressive wasting, and ultimately died from tuberculosis with much caseation at the site of the injection and in the regional lymph nodes. Histological examination of the excised portions of the parotid gland showed a striking increase in fibrous tissue, with little surviving gland and many endothelioid tubercles surrounded by zones of lymphocytic infiltration. Giant cells were scanty, there was no caseation, and tubercle bacilli were not found. The lachrymal gland was similarly affected, but to a less severe degree, and again tubercle bacilli were not found. Cavara gives a good summary of the literature, citing many cases similar to his own including that of Coppez (9), which showed an eruption of small vesicles on the bulbar conjunctiva which were tuberculous histologically; and he concludes that uveo-parotid fever is due to a special type of tuberculosis.

Writing on the subject in 1928, Roenne (41) stated that the eye changes are characteristic of tuberculosis both in their appearance and their prognosis, but pointed out that, though the characteristic parotitis had not in the literature been considered to be tuberculous, the fact that these two rare conditions occur together makes it certain that they have a common aetiology.

It is obvious from this review that the consensus of continental opinion is that uveo-parotid fever is due to tuberculosis; the English and American cases are few in number and show a greater diversity of opinion as to their aetiology. The first example of Heerfordt's syndrome recorded in this country was that of Brewerton (5) in 1910, followed by Mackay (30) in 1917, both being typical, with negative von Pirquet and Wassermann reactions. Mackay considered that it was not proved that mumps was the cause of the condition, and no mention is made of tuberculosis, but four years later he published a further note on his patient (31) describing the permanent eye changes. In 1921 Feiling and Viner (15) recorded a case showing evidence of peripheral neuritis, and in the same year Ramsay (38) noted another in which there had been cervical adenitis in childhood. This latter patient developed a nasal voice, regurgitation of fluids through the nose, and complete paralysis of the palate, though there is no suggestion that she was also suffering from diphtheria; the eye involvement was unusually severe. Two years later

Macbride (28) recorded a case in a woman aged forty-three, who had suffered from mumps as a child; in view of the frequency of facial palsy and the occasional occurrence of other evidence of nervous disease, he suggested the title of 'uveo-parotitic paralysis' and under this title Critchley and Phillips (10) reported a case from Bristol showing wasting of the small muscles of the hands and suspicious physical signs at the apices. They did not think that syphilis or mumps played any part in the aetiology, but believed that certain features of their case pointed to tuberculosis. Another example was seen in Bristol the same year and was recorded by Parker (36); he differentiated the condition from mumps, and was inclined to the view that one was dealing with an infective multiple neuritis, although the only nervous features in his case were right facial palsy and cyclopegia.

In 1927 another case was noted by McCulloch (29) in whom tubercles were seen along the periphery of both irides on slit-lamp examination; this case was also notable for the severity of the uveitis. Much the most important British paper came from Souter (47) in 1929, when he reported the case of a man aged forty with a family history of tuberculosis, but with negative tuberculin tests and absence of tubercle bacilli in the sputum on several occasions. Death resulted from miliary tuberculosis. Souter reviewed the literature and discussed the relationship of the syndrome to Mikulicz's disease. He referred to the tendency to favour a tuberculous pathology in Germany and Scandinavian countries, and emphasized the lack of definite ante-mortem evidence of tuberculosis in his case. He, nevertheless, associated himself with the continental view that tuberculosis is the predominant factor, 'a view contrary to that expressed in Britain and America'.

The next report was that of Kaitz (23) in 1931, and still another appeared in 1932 (Dorrell (13)), in which a biopsy of the parotid gave the histological picture of tuberculosis. With the exception of Souter and Dorrell, none of the more recent British authors has entered into the controversy as to aetiology with any very convincing argument.

There have been four American contributions to the literature, the first being Cutler's (11) in 1904 (before Heerfordt's original paper, but evidently a typical case); the next that of Jackson (22) in 1925, followed by Hamburger and Schaffer (19) in 1928, who concluded that 'tuberculosis is not the sole aetiological agent'. In 1931 Merrill and Oaks (32) summarized thirty cases including their own, though many others had been recorded by that time, including the very important case of Cavara, and the post-mortem study of Souter (47) and Thomson (49). After discussing mumps, syphilis, beri-beri, diphtheria, pseudo-leukaemia, oral sepsis, and tuberculosis as aetiological factors (without, however, mentioning the biopsy or post-mortem findings), they concluded that 'the weight of evidence to date points to some specific virus, bacterium, or agent as yet unknown'!

Uveo-parotid fever is attended by a low mortality, and though the post-mortem evidence is scanty it gives much support to the view that tuberculosis is the cause of the condition. Excluding the fatal case of Rogers,

Bodman, and Coombs (42) as not conforming to the description of the syndrome (uveitis was not present), only four deaths are reported. Lehmann's third case died later from pernicious anaemia a few weeks after the birth of a still-born child, and autopsy showed oedema of the lungs and changes typical of pernicious anaemia. No further information is given in her paper, but she was of the opinion that the pernicious anaemia had nothing to do with the uveo-parotitis. Of the remaining three, Bang's patient died from miliary tuberculosis and Souter's and our own showed identical autopsy findings with a widespread miliary tuberculosis and extensive tuberculous infiltration of the myocardium. Tuberculosis of the myocardium is a very rare condition, Carson (6) in 1928 being able to collect only eighty-seven cases from the literature, including his own. In reporting Souter's case one of us (Thomson (49)) added to Carson's list two more cases, bringing the number in 1930 to a total of ninety. Myocardial tuberculosis is generally classified as follows: (1) Large tubercles, single or multiple, which may project beneath the endocardium or pericardium or be buried in the myocardium; (2) The miliary variety, beneath the endocardium, more common in the walls of the ventricles; (3) Diffuse form; more or less generalized tuberculous infiltration of the myocardium usually accompanying tuberculous pericarditis. Both these cases come into the third and most uncommon group, and the occurrence of two extreme examples of this rare lesion in a condition which is itself rare cannot be dismissed necessarily as a pure coincidence. The two cases are in every way strikingly similar; in both the lesion is accompanied by miliary tuberculous pericarditis, and in both the tuberculosis is of a diffusely infiltrating, fibrosing type, without any caseation. In neither case was there any clinical sign or symptom of the cardiac condition, and in view of this and of the fibrosing nature of the tuberculous process we would suggest that it is not impossible that a similar lesion may have been present in some of the other cases of uveo-parotid fever, but, like the parotid lesion, healing spontaneously. The only way in which its existence might be suspected would be the occurrence of cardiac irregularity or heart-block from involvement of the conducting fibres, and unfortunately in neither case was an electrocardiogram taken. Thanks to the co-operation of Mr. Dorrell such an investigation was carried out in his case, with a perfectly normal result. We note that Altland (1) had made a diagnosis of chronic myocarditis in his case. We have been unable to see Berg's original paper, and the parotids were not examined in Souter's case, but there is no doubt that the parotitis in the present instance was of tuberculous origin, the lesion being of an endothelioid, non-caseating, and fibrosing nature. Though tuberculosis is associated with a characteristic histological picture, its individual elements are not always present in the same proportions; caseation and fibrosis may be marked or almost absent, and the number of endothelioid and giant cells may show great variation depending on the resistance of the patient and the virulence of the infection. We have examined the post-mortem material from Souter's case

as well as the section from the parotid in Dorrell's, and have been struck by the histological uniformity of the type of tuberculosis. Further, the photomicrographs of Dorrell's case (Figs. 9 and 10) are indistinguishable from those in Cavara's paper. In all the cases in which biopsies have been performed, whether from the parotids or from the irides, the histological features have been exactly similar, namely, an endothelial fibrosing tuberculosis in which caseation is absent and tubercle bacilli are not found. In our opinion this is no mere coincidence and explains many of the difficulties which stand in the way of the general acceptance of the tuberculous aetiology. It is evident from the type of the tuberculosis that either the resistance of these patients is very good or the tubercle bacilli are of unusally low virulence, since in spite of being infected by active tuberculosis these people are likely to overcome it successfully unless they are unfortunate enough to get a massive spread into the blood-stream when, as in the three reported fatal cases, they are likely to die of miliary tuberculosis.

Many of the authors who reject the tuberculous theory appear to do so mainly on the grounds that their own cases had no features suggestive of tuberculosis; but when both Souter's and our own show no obvious sign of tuberculosis, have negative von Pirquet reactions, and no family history (Souter's case had an uncle who died of consumption), and yet die of miliary tuberculosis, while the uveo-parotitis is still active, these objections, in spite of their formidable appearance, are no longer tenable. It may be suggested that although certain cases are undoubtedly tuberculous this does not apply to a significantly large enough number of them, but careful search in the literature, especially the recent German work, reveals the fact that the proportion is very much higher than many authors imagined, in our opinion high enough to put the matter beyond all doubt. We give below the results of our analysis, commencing with those cases in which there is definite evidence of tuberculosis:

1. *Post mortem.*
   - Bang, miliary tuberculosis.
   - Souter, miliary tuberculosis with tuberculosis of the heart.
   - Garland and Thomson, miliary tuberculosis with tuberculosis of the heart.
2. *Biopsies with histolological evidence of tuberculosis.*
   - (*a*) *Iris.*
     - Heerfordt (Case 1).
     - Altland.
     - Bang.
     - Fleischer (quoted by Berg).
   - (*b*) *Bulbar conjunctiva.*
     - Coppez.
   - (*c*) *Parotid.*
     - Weve (Cases 1 and 2).
     - Reimers.
     - Müller.
     - Cavara.
     - Dorrell.

We would stress the fact that in no case in which a biopsy was performed was histological evidence of tuberculosis lacking, a very significant finding.

3. *Iris nodules.* The only conditions which can give rise to similar nodules in the iris are syphilis and leprosy, both of which can be excluded. Many of these cases were indeed diagnosed as tuberculous iritis. We have not included any of the cases mentioned above, many of which also showed nodules in the iris.

Lehmann (Case 1).
McCulloch.
Uhthoff.
Schou.
Reith.

4. *Focal reaction to tuberculin (subcutaneously).*

Gjessing.
Thomsen.
(In addition to some already mentioned above.)

5. *Tuberculosis of the lungs with positive sputum.*

Lehmann (Case 2).

Thus in twenty-one cases, i.e., more than one-third of those recorded, we have incontrovertible evidence of tuberculous infection, which is hardly in keeping with Hamburger and Schaffer's categorical statement that 'it is only in some isolated instances that a strong probability of a tuberculous origin can be asserted'. In addition to these there are many others with features suggestive of tuberculosis, e.g. tuberculous family history (Kuhlefeld, Critchley, and Phillips), clinical or radiological signs of pulmonary tuberculosis (Berg, Schall, Mohr and Critchley, and Phillips); amenorrhoea (Ramsay); night sweats and lassitude (Leeksma, Case 1); pleural effusion (Merrill and Oaks); cervical adenitis (Kaitz); and those referred to later which have been successfully treated with tuberculin.

The von Pirquet test was noted in nineteen cases, of which only four were positive, but when there are included among the negatives two who died soon after the test from miliary tuberculosis and one in whom biopsies from the parotid and lachrymal glands were histologically positive and gave rise to tuberculosis in a guinea-pig (Cavara), we feel that no weight can be attached to such negative findings. In a recent review of the value of the tuberculin tests in man, Hart (20) draws attention to the relatively large error in the von Pirquet test and states that a negative reaction can never be relied upon for the exclusion of tuberculous infection.

There is no evidence to support Bang's theory of pseudo-leukaemia as the cause of uveo-parotitis, as blood examination, biopsy, and autopsy have all been consistently negative, and similarly there is no convincing evidence of a syphilitic basis. With regard to mumps we would only add to Lehmann's objections the fact that several patients had had mumps previously (Merill and Oaks, Hamburger and Schaffer, Schou, Kuhlefeld, and Macbride).

At this stage it is necessary to consider the relationship of uveo-parotid fever to Mikulicz's disease. In 1892 Mikulicz described a case of chronic, bilateral, painless enlargement of the salivary glands the cause of which was unknown. Since then many such cases have been reported, but these have shown such a variable pathology and clinical course that it is clear we must be dealing with a syndrome and not a disease. Cases have been described as being definitely due to leukaemia, lymphosarcoma, tuberculosis, syphilis, and pseudo-leukaemia, but there still remains a residue in which none of these conditions is present. This latter group Schaffer and Jacobsen (43) consider to be Mikulicz's disease proper, and due to a chronic low-grade infection running a slow course with spontaneous recovery. In the symptomatic group, with a specific aetiology, they included Heerford's syndrome, and record as a case of Mikulicz's disease the case subsequently reviewed by Hamburger and Schaffer (19) as a case of uveo-parotitis. Further, Weve (53) used the term 'Mikulicz–Heerfordt' for his two familial cases. Reimers (39), on the other hand, pointed out that certain cases of Miculicz's disease are due without doubt to tuberculosis, which when complicated by uveitis are indistinguishable (apart from the lachrymal swelling) from uveo-parotitis. While agreeing with this, we entirely disagree with the views of Schaffer and Jacobsen, as we can find only nine examples of uveo-parotitis with lachrymal involvement, and it is only these that can be legitimately called Mikulicz's syndrome. Heine (quoted by Cavara (7)) saw eight cases of Mikulicz's disease with ocular complications of which four were certainly tuberculous, and of these three had uveitis and the fourth 'tuberculous conjunctivitis'. Three similar cases are reported by Fuchs (16) all having enlargement of both lachrymals and parotids as well as bilateral iridocyclitis.

Nervous Phenomena

The only common nervous lesion in uveo-parotid fever is facial palsy (about 50 per cent.), and we agree with Reimers, Berg, Thomsen, Schall, and others that this is due to direct involvement of the nerve in the parotid lesion. The fact that the paralysis is often limited to the lower part of the face and that taste has only been impaired in one case (Daireaux and Péchin) certainly points to a peripheral lesion of the nerve. Some authors object to this view on the ground that the facial palsy is not always synchronous with the parotitis, in some cases apparently preceding it; but as the lesion frequently commences in the pre-auricular portion of the gland, at the site of entry of the facial nerve, it is conceivable that the earliest swelling had escaped the patient's notice. Palsy developing when the parotitis is subsiding (Reith (40)) is probably due to the cirrhotic nature of the inflammatory lesion.

Dysphagia has been considered to be evidence of cranial nerve paralysis by many authors, but as it has usually been accompanied by dryness of the

mouth, it is, in our opinion, due to the lack of salivary secretion resulting from the parotitis rather than to nervous dysfunction.

The remaining signs and symptoms of nervous disease have been ascribed to polyneuritis, which is a well-known complication of an active tuberculous focus and can, we think, be explained in this way. Although cerebrospinal nerve palsies were said by Heerfordt to be a frequent complication of the disease, there is no convincing evidence of a lesion of any but the seventh cranial nerve, and we do not think that any other nervous disorder is commonly seen in this syndrome.

Prognosis

The mortality in uveo-parotid fever is low, only three cases having died from the disease (about 5 per cent.). There is usually no permanent impairment of general health and the parotitis and facial palsy almost invariably recover. The outlook in respect of the ocular lesions is more variable. In many cases there is permanent impairment of visual acuity, which may be severe; relapses are not infrequent and blindness may develop.

Treatment

In view of the sclerosing nature of the tuberculosis with its great tendency towards spontaneous healing, the value of any treatment is difficult to assess; but many authors claim striking improvement as a result of tuberculin therapy (Lehmann, Fleischer, Schall, Thomsen, and Uhthoff), while others advocate the use of X-rays or radium (Hamburger and Schaffer) for the parotitis. But as the parotitis resolves spontaneously the treatment should probably be that of tuberculous iritis combined with general treatment for tuberculosis.

Summary and Conclusions

Uveo-parotid fever (Heerfordt) is a well-defined clinical and pathological entity, characterized by bilateral uveitis and parotitis, pursuing a chronic course with a well-marked tendency to spontaneous recovery. Death, in the rare instances in which it occurs, is due to miliary tuberculosis. Facial palsy occurs in half the cases, and in one-third there is slight pyrexia at some stage. The cause of the condition is tuberculosis of a particularly fibrosing and non-caseating type, and in a certain number of cases the myocardium is similarly affected. Manifestations of polyneuritis are infrequent and form no essential part of the disease. 'Uveo-parotid tuberculosis' is suggested as a more suitable title than either 'febris uveo-parotidea subchronica' or 'uveo-parotitic paralysis'.

We wish to express our thanks to Dr. Maxwell Telling and Mr. S. D. Lodge for permission to use the clinical notes of this case, to Professor M. J. Stewart for the post-mortem report, to Mr. W. C. Souter for the loan of Fig. 2, and to Mr. E. A. Dorrell for the section from which Figs. 9 and 10 were prepared.

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DESCRIPTION OF PLATES

FIG. 1. Tuberculous infiltration of the myocardium in uveo-parotitis. A transverse section of the heart showing the greater part of the right ventricle and a large part of left replaced by lighter coloured tuberculous granulation tissue.

FIG. 2. Tuberculous infiltration of the myocardium in uveo-parotitis. The thoracic organs of Souter's case with the left ventricle laid open. Note the striking similarity between this case and our own in the type and extent of the myocardial tuberculosis, although the distribution is somewhat different.

FIG. 3. Tuberculosis of the myocardium. The very cellular infiltrating nature of the lesion is evident (× 65).

FIG. 4. Tuberculosis of the myocardium. A high-power view of the same section; typical tuberculous tissue without caseation (× 380).

FIG. 5. Right parotid gland. There is marked fibrosis with little surviving glandular substance, best seen in the pre-auricular part of the gland (upper part of section). The two darkly staining masses in the lower right corner are lymph nodes and are not involved in the fibrosis (× 3).

FIG. 6. Left parotid gland. A similar but less marked lesion is present.

FIG. 7. Right parotid gland. A section through one of the fibrosed areas showing a duct surrounded by tuberculous granulation tissue (× 105).

FIG. 8. Right parotid gland. A small tuberculous focus from the edge of the gland showing two adjacent tubercle follicles with large giant cells (× 65).

FIG. 9. A low-power view of the parotid in Dorrell's case. Extreme endothelioid tuberculosis is present. The few surviving parotid acini and ducts stain more deeply and show some lymphocytic infiltration. The tuberculous tissue is uniformly cellular and caseation is absent (× 65)

FIG. 10. A high-power view of a tubercle follicle from the same section, showing a giant cell and many endothelioid cells surrounded by a zone of lymphocytes (× 380).

FIG. 1

FIG. 2

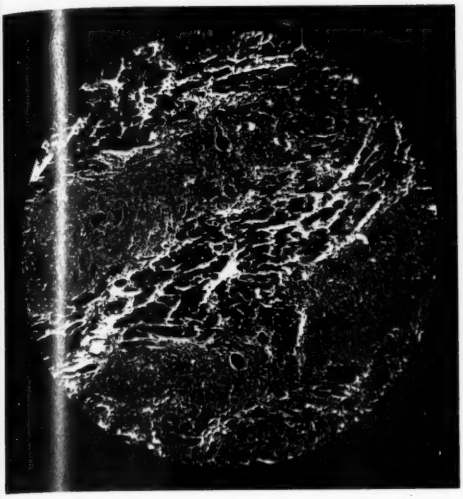

FIG. 3

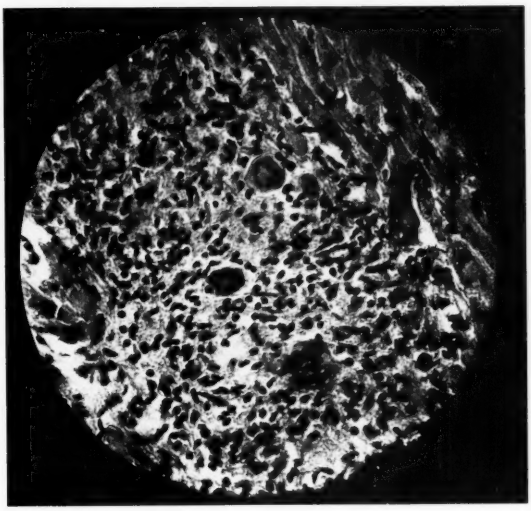

FIG. 4

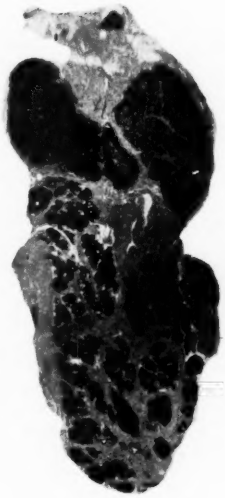

FIG. 5

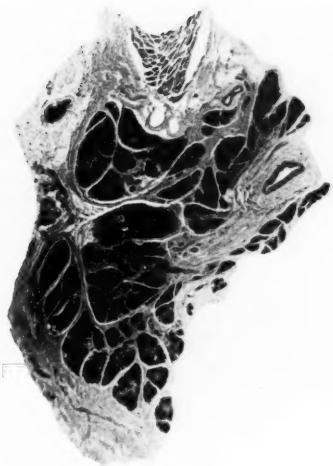

FIG. 6

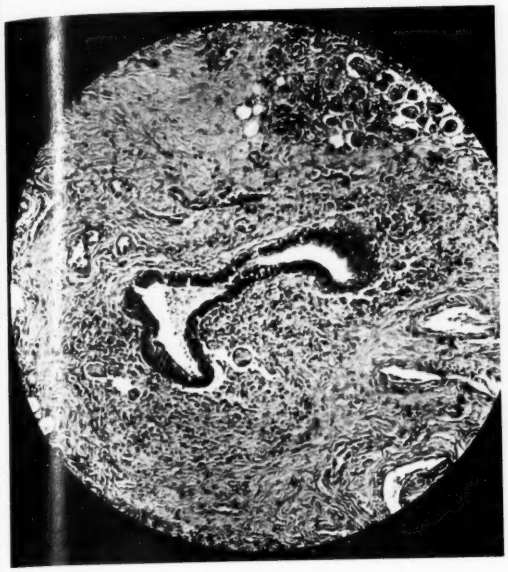

FIG. 7

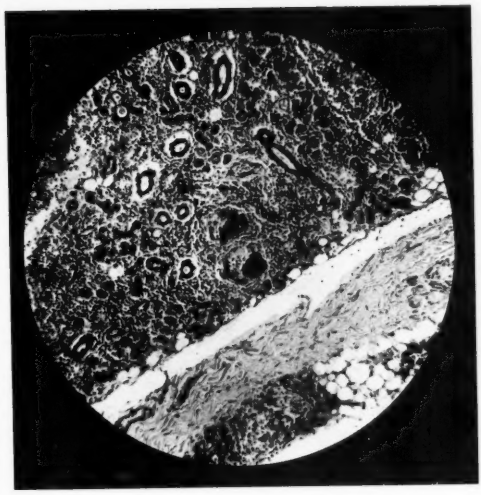

FIG. 8

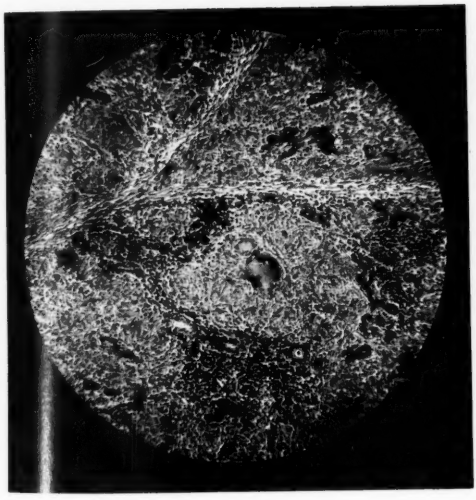

FIG. 9

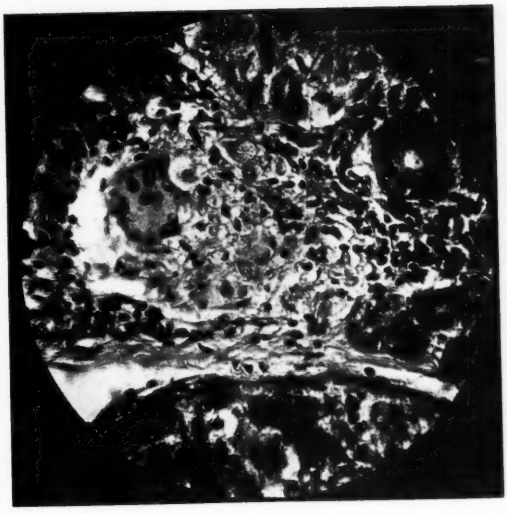

FIG. 10

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616.25–003.219–08

THE VALUE OF ARTIFICIAL PNEUMOTHORAX IN PULMONARY TUBERCULOSIS[1]

By CEDRIC SHAW

The evaluation of a therapeutic agent is perhaps more difficult in pulmonary tuberculosis than in any other disease. In pulmonary tuberculosis clinical impressions largely must form the foundation upon which conviction is built; but conviction built on such a foundation is not a matter of reason alone, and it is right that it should be reinforced by some factor more free from personal bias. An experience of statistical dimensions, actuarially treated, would satisfy this need; but its achievement, however, is practically impossible. The analysis of an experience, which though not large, is significant, can at least temper clinical impressions. This is my excuse for presenting a study of so small a material as 267 cases of pulmonary tuberculosis which have been treated by artificial pneumothorax between the years 1922 and 1930.

The cases have been under the care of Dr. Batty Shaw at the Brompton Hospital, and have later attended his out-patient artificial pneumothorax clinic, of which I was in charge; the minority have had their lungs collapsed elsewhere and have subsequently been sent to the clinic for a continuance of treatment.

The one real 'ponderable' in pulmonary tuberculosis is mortality, and it is proposed to attempt an evaluation of A.P. therapy by comparing the mortality amongst the A.P. cases with that experienced after pure sanatorium treatment, as shown by Bardswell and Thompson's 'Pulmonary Tuberculosis: Mortality after Sanatorium Treatment', *Med. Res. Coun. Spec. Rep.* No. 33(1), i.e. the 'Midhurst Report' of 1919. This report has been chosen because there is less numerical discrepancy between the number of cases upon which it is based—1,707—and the small number of cases dealt with in this paper. The report by Trail and Stockman (2) in 1931 has not been chosen because it shows no mortality rates for the aggregate material.

The results disclosed by the Midhurst Report can be considered as fairly representative of sanatorium results in general, as the following comparison with other similar publications will show. The ratio of actual to expected deaths is used as the basis of comparison.

[1] Received December 1, 1932.

Sanatorium.	Ratio of actual to expected deaths.			
	Gp. I cases.	Gp. II cases.	Gp. III cases.	All groups.
Midhurst (1)	5·8	16·6	38·5	16·5
Frimley (3)	3·9	16·1	46·7	17·1
Adirondack (5)	3·1	10·8	41·4	18·7
Grefsen (4)	2·7	7·5	27·5	12·0

The close similarity of the Midhurst and Frimley results, despite the disparity in the social status of the patients admitted to these sanatoria, has been detailed in the Hartley, Wingfield, and Thompson report of 1924. The small differences between the English and the American and Norwegian ratios is explained by the use of different life tables for their calculation—English Life Table No. 8 in the case of Midhurst and Frimley, English Life Table No. 6 and the Norwegian Life Table respectively for the others.

Though the indications for the induction of an artificial pneumothorax have been widened in recent years, it is still maintained by most tuberculosis physicians that it is unjustifiable, in the ordinary case, to initiate the treatment until the patient has been subjected to, and has failed to respond to, a preliminary period of sanatorium régime. Dr. Batty Shaw has adopted an attitude different from this conservative one, namely, that if in the moderately well-to-do clinical, bacteriological, and skiagraphic methods of control show that sanatorium methods are not effecting arrest, say within three months, A.P. treatment should be carried out; but for the wage-earner, especially indoors, the parents of young children, and the poor, A.P. treatment should be given when the diagnosis is confirmed by bacteriological and/or X-ray manifestations.

Thus this paper deals with a material different from that with which previous published results of pneumothorax therapy have dealt, in that it contains a percentage of early cases which in other hands would not have been subjected to lung collapse.

Comparison of the A.P. Material with the Midhurst

For the purposes of comparison the cases have been classified clinically in the same way as the Midhurst (classification of Nat. Tub. Assoc. of America), which is:

Group I. Incipient cases. Slight or no constitutional symptoms, particularly gastric or intestinal disturbances, or rapid loss of weight. Slight or no elevation of temperature or acceleration of pulse at any time during the twenty-four hours. Expectoration small in amount or absent; tubercle bacilli may or may not be present. Slight infiltration limited to the apex of one or both lungs, or to a small part of one lobe. No tuberculous complications.

Group II. Moderately advanced cases. No marked impairment of function, either local or constitutional. Marked infiltration, more extensive than in the incipient cases, but with little or no evidence of cavity formation. No serious tuberculous complications.

Group III. Far advanced cases. Marked impairment of function, both local and constitutional. Extensive infiltration or consolidation in one or more lobes, or disseminated areas of cavity formation or serious tuberculous complications.

In all but two of the A.P. cases, there has been radiological confirmation of the diagnosis, and the clinical grouping, with regard to the extent and type of disease, has been dependent on the radio-anatomical findings, and not upon physical signs alone, as would seem to be the rule with the Midhurst cases. The points of similarity and dissimilarity between the two are shown in the appended tables and figures.

Sex Distribution

	Total number of patients.	Number of		Percentage of	
		Males.	Females.	Males.	Females.
Present series	267	139	128	52	48
Midhurst	1707	1053	654	61	39

Clinical Grouping of A.P. Material

	Number of		Percentage of	
	Males.	Females.	Males.	Females.
Group I	22	21	15·8	17·2
Group II	68	55	48·9	43·0
Group III	49	52	35·3	39·8
	139	128	100·0	100·0

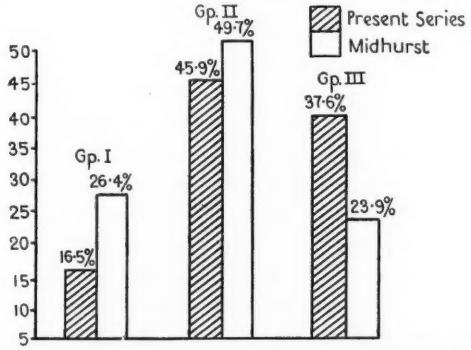

FIG. 1. Comparison of percentages in each group with Midhurst. Sexes are combined.

Distribution in Age Groups

Age group.	Number.				Percentage.			
	Present series.		Midhurst.		Present series.		Midhurst.	
	Males.	Females.	Males.	Females.	Males.	Females.	Males.	Females.
–22	35	46	127	77	25·2	35·5	12·1	11·8
23–27	27	44	249	166	19·4	34·3	23·6	25·4
28–32	20	12	219	157	14·4	9·7	20·8	24·0
33–37	26	14	185	107	18·7	10·9	17·6	16·3
38–42	15	5	120	70	10·8	3·9	11·4	10·7
43–	16	7	153	77	11·5	5·7	14·5	11·8
	139	128	1053	654	100·0	100·0	100·0	100·0

A Comparison of the Positive Sputum Incidence; Present Series

	Group I		Group II		Group III	
	M.	F.	M.	F.	M.	F.
T.B. positive	18	6	58	47	49	48
T.B. negative	4	15	10	8	—	4

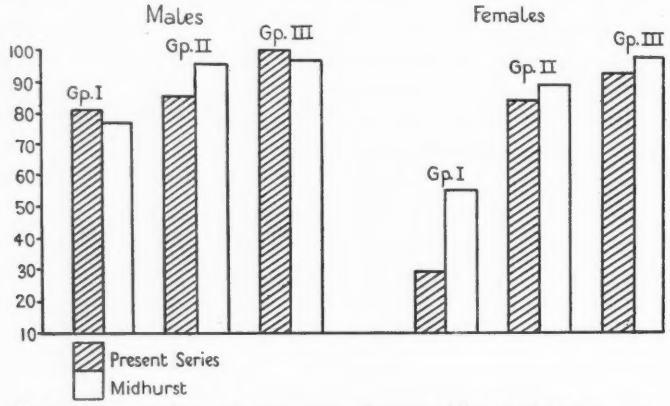

FIG. 2. Comparison of percentage of cases with a positive sputum.

It will be seen that the present series contains 9 per cent. fewer males than the Midhurst. It also shows a smaller proportion of early cases, and a greater of 'far advanced', whilst so far as the age-group distribution is concerned, the age groups –22, 23–27 are proportionately more strongly represented in the A.P. experience, especially on the female side. In the percentage incidence of a positive sputum, the two experiences are very similar.

Thus what qualitative differences there exist between the two experiences should militate adversely to the A.P. with regard to mortality (*vide* MacNalty (6)). In reference to social status also, the advantage is on the side of Midhurst, which admits the middle and upper classes only, whilst the bulk of this series is drawn from the artisan, labourer, clerk, and other working classes, with a small sprinkling of the type for which Midhurst caters.

Further Data of the Cases

The greater number of the patients dealt with have passed through Brompton, most of them to Frimley or the Ventnor sanatorium, a few to other sanatoria; some never went to a sanatorium at all, and a few never went through the hospital, but were transferred from the sanatorium where the A.P. was induced to our out-patient clinic. This table shows the relative number in each of these categories:

	Group I.	Group II.	Group III.
Brompton and Frimley	17	61	45
Brompton and other San.	5	23	19
Brompton only: no San.	21	33	29
Sent from Sanatorium	—	6	8
	43	123	101

The importance of the degree of collapse obtained, upon the results of treatment has been stressed by Rist, Gravesen, the Matsons, and many others. In this analysis each case has been assigned to one of three classes of collapse—'complete', 'satisfactory incomplete' (i.e. where, despite the presence of adhesions, a sufficient degree of collapse to control symptoms has been achieved), and 'unsatisfactory'. The number in the last group is negligible since almost all of such cases have been weeded out before they reached the clinic:

	Complete.	Satisfactory incomplete.	Unsatisfactory.
Group I	19	24	—
Group II	47	76	—
Group III	26	73	2

The side of the A.P. and the duration of treatment are shown in the following tables:

Right.	Left.	Bilateral.	Uni- then bilateral.	Consecutive.
136	98	14	8	11

Years	0–½	½–1	1–1½	1½–2	2–3	3–4	4–5	5 upwards
Cases	9	18	47	46	71	54	13	9

The complications, tuberculous and non-tuberculous, present before the inception of treatment were:

	Group I.	Group II.	Group III.
Tuberculous			
Laryngeal infection	—	13	14
Ischio-rectal abscess	—	1	1
Larynx + isch. rectal abscess	—	1	—
Cervical adenitis	—	1	—
Epididymitis	—	—	1
Non-tuberculous			
Slight mental deficiency	1	—	—
Rheumatoid arthritis	—	1	—
Gastric ulcer	—	3	—
Diabetes	—	—	1
Asthma	—	1	—

Sixty-two of the cases are still under treatment; the mode in which treatment was terminated in the rest was:

	Group I.	Group II.	Group III.
End of treatment	20	23	13
Obliterated	6	46	21
Purulent effusion	2	8	11
Contralateral spread or increase	—	8	38
Fatal spon. pneumothorax	—	—	2
Fatal pleural shock	—	1	—
At patient's request	—	1	3
Still being refilled	13	36	13
Accidental death	1	—	—
Not known	1	—	—

In only a very few cases was any form of active treatment used in addition to A.P.

	Group I.	Group II.	Group III.
Gold	—	2	—
Homolateral phrenic evulsion	—	3	2
Contralateral phrenic evulsion	—	1	—
Thoracoplasty	—	—	2
Cauterization of adhesions	—	—	5

The complications encountered during the course of treatment were:

	Group I.	Group II.	Group III.
Serous effusion	9	26	27
Purulent T.B. negative effusion	—	3	1
Purulent T.B. positive effusion	2	5	7
Pneumococcal empyema	—	—	1
B. Friedlander empyema	—	—	1
Fatal pleural shock	—	1	—
Non-fatal pleural shock	—	—	1
Fatal spontaneous pneumo.	—	—	2
Non-fatal spontaneous pneumo.	—	1	—
Spon. pneumo. + T.B. neg. effusion	—	—	2
Spon. pneumo. on one side and T.B. pos. eff. and pleuro-bronchial fistula on the other	—	—	1

The percentage incidence of these complications was:

	Group I.	Group II.	Group III.
Serous effusion	21	21	27
Purulent effusion	5	6·5	10
Pleural shock	—	·75	1
Spontaneous pneumo.	—	·75	5

The incidence of serous effusions is smaller than that given by most observers, but this is because only those of significant size have been considered.

In Groups II and III 25 per cent. and 80 per cent. respectively of the patients who developed a purulent effusion have died. Also in two of the five cases of spontaneous pneumothorax in Group III death has ensued. It will be noticed that both these complications become progressively more common from Group I to Group III.

Much stress has been laid by all observers upon the state of the contralateral lung, and a consideration of this factor is important for an assessment of the material:

Group I.

Other lung not infected . . . . . 31 cases
,, ,, radiologically suspicious . . . . 5 ,,
,, ,, infected . . . . . 7 ,,*

*(1 fibrosed apex, 6 scattered old infiltration of one zone.)

Group II.

Other lung not infected . . . . . 53 cases
,, ,, radiologically suspicious . . . . 17 ,,
,, ,, infected . . . . . 53 ,,

Zone.	*Radiological Type of Disease.*	
Upper	Fibrosis	4 cases
	Infiltration	8 ,,
Middle	Infiltration	18 ,,
Upper and middle	Fibrosis	1 ,,
	Infiltration	20 ,,
Lower	Infiltration	1 ,,
All	Very scattered infiltration	1 ,,
		53

Group III.

Other lung not infected	10 cases
,, ,, radiologically suspicious	7 ,,
,, ,, infected	84 ,,

Zone.	*Radiological Type of Disease.*	
Upper	Fibrosis	2 cases
	Infiltration	5 ,,
Middle	Infiltration	13 ,,
Upper and middle	Infiltration	37 ,,
	Infiltration and softening	10 ,,
Middle and lower	Infiltration	3 ,,
All zones	Infiltration and excavation	5 ,,
	Infiltration	9 ,,
		84

It is apparent that in Group I the importance of the contralateral disease is small. In Group II 43 per cent. showed disease of the 'better' lung, this being made up by:

Fibrosis	4 per cent.
Infiltration of one zone	22 ,,
Infiltration of two or more zones	17 ,,

In Group III 84 per cent. of the cases had contralateral disease thus:

Fibrosis	2 per cent.
Infiltration of one zone	18 ,,
Infiltration of two zones	40 ,,
Infiltration of two zones with softening	10 ,,
Infiltration of all zones	9 ,,
Infiltration of all zones with excavation	5 ,,

Results

When this inquiry was undertaken, a questionary and a request to attend at the clinic again was sent to every surviving patient, and a list of those who had died was submitted to the Registrar-General's department for documentary evidence of the date and certified cause of death; this list

included also those who were untraced, and in no case has a certification of death been found. The methods by which information of the present condition of each patient was obtained may be classified as follows:

Deaths	62 cases
Still under treatment	62 ,,
Personal attendance at clinic (therefore bacteriological and radiological evidence of present condition)	55 ,,
Replied to questionary only	81 ,,
Untraced—death not certified	7 ,,
	267

The results of this experience are analysed according to the mortality and the working capacity and symptoms of the survivors. The mortality is then compared with that shown by the Midhurst report. Each clinical group is treated separately.

Group I. Mortality

	Males.	Females.
Untraced	2	—
Killed in a motor accident three months after A.P.	1	—
Alive	19	21
Dead	—	—
	22	21

Group I. Working Capacity of Survivors

	Males.	Females.
At full work	18	18
Fit for work, but unable to find work, or non-workers	1	3
	19	21

Group I. Symptoms of Survivors

	Males.	Females.
Completely symptomless	14	21
Sl. morning cough and no or negative sputum	4	—
Cold abscess of chest wall only	1	—
	19	21

Period of Observation

Years	½–1	1–1½	1½–2	2–3	3–4	4–5	5–6	6–7
Cases	2	1	1	9	15	11	2	2

Group II. Mortality

	Males.	Females.
Untraced	—	2
Alive	61	47
Dead	7	6
	68	55

All of the deaths were certified as due to pulmonary tuberculosis, and in one case to tuberculous enteritis as well.

Group II. Working Capacity of Survivors

	Males.	Females.
At full work	52	33
Fit for, but unable to find work, or non-workers	3	9
Unfit for work, or for part time only	2	4
Undergoing institutional treatment	4	1
	61	47

Group II. Symptoms of Survivors

	Males.	Females.
Completely symptomless	41	36
Sl. cough and negative sputum	12	5
Cough and positive sputum—no toxaemia	7	4
Considerable symptoms	1	2
	61	47

Period of Observation

Years	½–1	1–1½	1½–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–
Cases	2	—	8	30	31	17	13	8	6	6	2

Group III. Mortality

	Males.	Females.
Untraced	3	—
Alive	23	27
Dead	23	25
	49	52

Group III. Certified Causes of Death

	Males.	Females.
Pulmonary tuberculosis	18	21
Tuberculous broncho-pneumonia	1	—
Tuberculous meningitis	1	—
Tuberculous enteritis	1	1
Tuberculous empyema	—	1
Haemoptysis	1	—
Spontaneous pneumothorax	—	2
Suicide	1	—
	23	25

Group III. Working Capacity of Survivors

	Males.	Females.
At full work	13	15
Fit for, but unable to find work, or non-workers	3	5
Undergoing home or institutional treatment	7	7
	23	27

Group III. Symptoms of Survivors

	Males.	Females.
Completely symptomless	12	18
Slight cough and negative sputum	2	1
Slight cough and scanty positive sputum—no toxaemia	2	1
Cough, positive sputum and toxaemia	7	7
	23	27

Period of Observation

Years	½–1	1–1½	1½–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9
Cases	7	9	11	27	19	13	3	6	2	4

A comparison can now be made between the mortality in the present series, and that in the Midhurst.

Total Mortality

	Number of cases.		Number dead.		Percentage dead.	
	M	F	M	F	M	F
Present series	139	128	30	31	21·5	24·2
Midhurst	1053	654	478	273	45·3	41·7

Group I. Mortality

	Number of cases.		Number dead.		Percentage dead.	
	M	F	M	F	M	F
Present series	22	21	—	—	—	—
Midhurst	289	171	67	23	23·1	13·5

Group II. Mortality

	Number of cases.		Number dead.		Percentage dead.	
	M	F	M	F	M	F
Present series	68	55	7	6	10·3	10·9
Midhurst	541	307	245	131	45·3	42·7

Group III. Mortality.

	Number of cases.		Number dead.		Percentage dead.	
	M	F	M	F	M	F
Present series	49	52	23	25	46·9	48·0
Midhurst	223	176	166	119	74·4	67·6

The material of the present series has been submitted to Brian Harley, A.I.A., and he has constructed tables of the rates of mortality for comparison with the Midhurst. He has adopted the same and standard actuarial principles as those fully set forth in Appendix B of the Midhurst report. I am indebted to him for the following statements.

The observation period extends from April, 1922, to August, 1932; it began in each case with the date of the induction of the A.P. and ended with the last date to which it could be traced; this ranged from May, 1931, to August, 1932. If a fixed point such as May, 1931, is taken for the cessation of observation, mortality rates are obtained which differ insignificantly from those obtained by the method decided upon. The average age at the time of induction of artificial pneumothorax was 31 years for males, 27 for females, and 29 for the combined sexes: the range of ages was from 14 to 51 years; in the Midhurst experience (1907–16) the average age for each sex was over 32 years, and the range was from 14 to 66. The present series is small, based on 1,002 years of life, passed through by 260 persons. Seven other untraced cases, which would have contributed only about six years of experience, were excluded from the mortality investigation.

The following tables compare the mortality rates, first for the combined clinical groups and then for Group III alone; it is perhaps only in this group that the deaths in this series attain significant numbers.

A review of the tables shows a wide dissimilarity between the mortality rates, the advantage lying, in nearly every year of duration and in the average rates for all durations, emphatically with the present series. It will be noticed that the differences between the respective ratios of actual to expected deaths are not so wide. This is because the ages are some three or four years younger than those of the Midhurst experience; thus the expected deaths by the Standard Table are lowered, and the ratios correspondingly increased. If for both experiences the same average age is used, then a comparison of the ratios of actual to expected deaths in the two again shows a considerable dissimilarity in favour of this series.

A Comparison of the Mortality Rates for Males (all Clinical Groups)

	Present series.					Midhurst.				
Duration.	Exposed to risk.	Actual deaths.	Expected deaths.	Ratio act. exp.	Rate of mortality.	Exposed to risk.	Actual deaths.	Expected deaths.	Ratio act. exp.	Rate of mortality.
0	134	1	0·7	1·4	0·007	1048	163	6·8	23·8	0·155
1	133	8	0·7	11·4	0·060	874	117	6·0	19·5	0·134
2	106	9	0·6	15·0	0·085	646	74	4·7	15·8	0·115
3	65	8	0·4	20·0	0·123	499	52	3·8	13·7	0·104
4	36	3	0·2	15·0	0·083	392	32	3·1	10·3	0·082
5	24	2	0·2	10·0	0·083	285	17	2·4	7·2	0·060
6	11	—	0·1	—	—	212	13	1·9	6·9	0·061
7	11	—	0·1	—	—	132	6	1·3	4·8	0·045
8	3	—	—	—	—	56	4	0·6	7·2	0·071
9	—	—	—	—	—	—	—	—	—	—
	523	31	3·0	10·3	0·059	4144	478	30·5	15·7	0·115

A Comparison of the Mortality Rates for Females (all Clinical Groups)

	Present series.					Midhurst.				
Duration.	Exposed to risk.	Actual deaths.	Expected deaths.	Ratio act. exp.	Rate of mortality.	Exposed to risk.	Actual deaths.	Expected deaths.	Ratio act. exp.	Rate of mortality.
0	126	5	0·5	10·0	0·040	651	82	3·3	25·2	0·126
1	120	11	0·5	22·0	0·092	564	73	3·0	24·9	0·129
2	91	6	0·4	15·0	0·066	426	53	2·3	23·0	0·124
3	64	4	0·3	13·3	0·063	325	31	1·8	16·8	0·095
4	36	4	0·2	20·0	0·111	253	14	1·5	9·1	0·055
5	22	—	0·1	—	0·000	186	15	1·2	12·2	0·080
6	14	1	0·1	10·0	0·071	136	3	1·0	3·2	0·022
7	6	—	—	—	—	90	1	0·6	1·6	0·011
8	—	—	—	—	—	44	1	0·3	3·1	0·023
9	—	—	—	—	—	—	—	—	—	—
	479	31	2·1	14·8	0·065	2675	273	15·0	18·2	0·102

A Comparison of the Mortality Rates for Both Sexes and All Groups

Duration.	Present series. Exposed to risk.	Actual deaths.	Expected deaths.	Ratio act. exp.	Rate of mortality.	Midhurst. Exposed to risk	Actual deaths.	Expected deaths.	Ratio act. exp.	Rate of mortality.
0	260	6	1·2	5·0	0·023	1699	245	10·1	24·2	0·144
1	253	19	1·2	15·8	0·075	1438	190	8·9	21·3	0·132
2	197	15	1·0	15·0	0·076	1072	127	7·0	18·2	0·118
3	129	12	0·7	17·3	0·093	824	83	5·6	14·7	0·100
4	72	7	0·4	17·5	0·097	645	46	4·6	9·9	0·071
5	46	2	0·3	6·7	0·043	471	32	3·6	8·9	0·068
6	25	1	0·2	5·0	0·040	348	16	2·8	5·6	0·046
7	17	—	0·1	—	—	222	7	1·9	3·7	0·032
8	3	—	—	—	—	100	5	0·9	3·7	0·050
9	—	—	—	—	—	—	—	—	—	—
	1002	62	5·1	12·2	0·062	6819	751	45·5	16·5	0·110

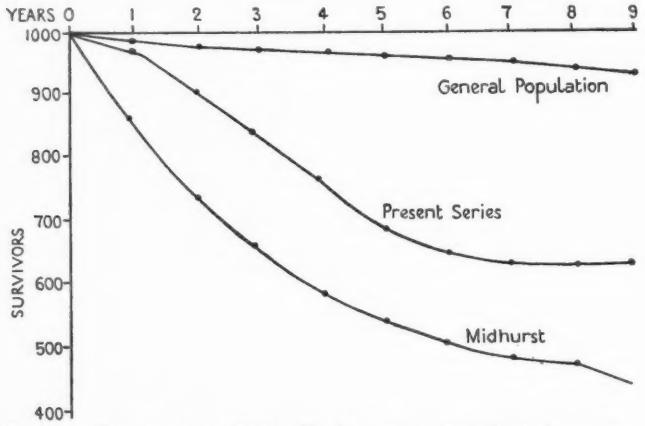

FIG. 3A. Survivors per 1000. Both sexes and all clinical groups.

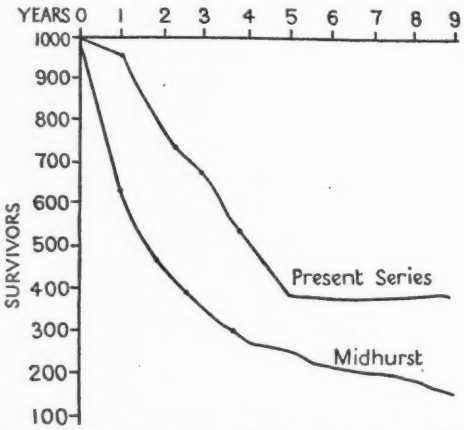

FIG. 3B. Survivors per 1000. Both sexes: Group III only.

A Comparison of the Mortality Rates for Both Sexes in Group III only

Duration.	Present series.			Midhurst.		
	Exposed to risk.	Deaths.	Rate of mortality.	Exposed to risk.	Deaths.	Rate of mortality.
0	98	4	0·040	396	148	0·374
1	94	18	0·191	245	67	0·273
2	68	10	0·147	148	31	0·209
3	43	10	0·233	97	17	0·175
4	25	6	0·240	72	6	0·083
5	13	—	—	53	10	0·189
6	7	—	—	35	3	0·086
7	6	—	—	25	1	0·040
8	1	—	—	10	2	0·200
9	—	—	—	—	—	—
	355	48	0·135	1081	285	0·264

Discussion of Data

The series consists of clinically- and radiologically-proved cases of pulmonary tuberculosis, with an average positive sputum incidence of 80 per cent. All but two of the cases have had a complete or a satisfactory incomplete collapse of the lung; in nine cases only has the period of treatment been under a year. It is a pure material in the sense that the incidence of non-tuberculous complications, and the use of adjuvant methods of treatment, except sanatorium, has been negligible. The observation period has been adequate to the extent that, for the majority of the cases, it has been more than two to three years, which, as both A.P. and sanatorium reports testify, is the peak region for mortality after treatment. It is a satisfactory material for review also, because only 62 of the 267 patients are still under treatment, and only 7 have not been traced, and of these there is no documentary evidence of death.

In its variety the material differs from that which has formed the substance of other reports on pneumothorax therapy. In these cases the indications for the induction of a pneumothorax have been far wider than the conventional; in the early case, pneumothorax has been used as the most rational method for attaining the lung-rest which is the primary factor in the arrest of the disease; in the far-advanced it has been used as the most certain means of prolonging life and palliating suffering. But that the results have not been influenced by an unduly high proportion of early and mild cases is demonstrated by the fact that in Group II 43 per cent. and in Group III 84 per cent. of the cases showed a varying degree of infection of the contralateral lung. It is this variety which makes this series a qualitative miniature of the Midhurst. What differences there exist between the two in clinical grouping and age-group distribution have been shown to be unfavourable to the present series when viewed from the standpoint of probable mortality. Yet a scrutiny of the tables showing the mortality relative to each experience evinces results for the A.P. which can justly be described as overwhelmingly superior.

Thus, whilst in Group I—the minimal cases—there are no deaths, the mortality for the sanatorium reaches 23·1 per cent. for males and 13·5 per cent. for females. It must be remarked here that in the Midhurst Group I 22·5 per cent. of the males and 45·6 per cent. of the females at no time were found to have tubercle bacilli in the sputum, and since there is no mention of the employment of radiology, the correctness of the diagnosis in a certain number of these sputum negative cases must be open to question. It is thus possible that the percentage mortality in this group at Midhurst was actually higher than that shown—and the difference between the results in this group, in the two series, therefore the more striking. In Group II the mortality after sanatorium treatment is more than four times greater than that after pneumothorax. In Group III the mortality after sanatorium treatment is approximately 50 per cent. greater than that after pneumothorax. The methods of the statistician corroborate these arguments, for taking all clinical groups together and Group III alone, the mortality rate for males and females, separately and combined, in this series is roughly half that in the sanatorium.

Because of the smallness of both series it is not possible to prove a superiority of A.P. therapy over sanatorium treatment, but, clinical group for clinical group, the statistical differences between the two are so striking that they convey an impression that active intervention is preferable to the policy of the sanatorium.

Although the superiority of A.P. therapy over those given by the more conservative methods of treatment is indicated by other observers—they have insisted upon an initial trial of sanatorium régime—all appear to deprecate the active treatment of early cases. All the French authorities—Rist (7), Rist and Hirschberg (8), Pissavy (9), Bonin (10), Dumarest and Brette (11)—make a feature of the unilaterality or the advanced degree of the disease, as almost a *sine qua non* for the induction of a pneumothorax. Gravesen (12) and Saugman (13) are insistent upon the necessity for a preliminary period of non-reaction to sanatorium measures, and treat mostly Turban-Gerhardt St. III cases. In America the Matsons and Bisaillon (14, 15) in their publications also insist upon the preliminary trial of conservative measures, and advise the treatment chiefly in what corresponds to our Group III cases. Swezey and Schonbar (16) agree with this policy, as does Andrew Peters (17). Amberson (18) insists on the unilateral nature of the disease as the main indication. Leroy Peters (19) gives no data at all; and the declarations of Fishberg (20) may be dismissed as unsupported by evidence. Amongst the German observers—Maendl (21), Raykowski (22), Epstein (23), Sachs (24), Jessen (25), Weissner and Wolff (26), Baumann (27), Harms and Grundewald (28)—the last four papers alone give any data of the type of material upon which they are reporting; they treat advanced cases only. In England, Pearson (29) treats no early cases, and considers the induction of an A.P. unjustifiable without an initial phase of pure sanatorium treatment. Macfie and Alexander (30) concur and treat advanced cases only. Trail and

Stockman (31), in an experience of 91 cases corresponding to Groups II and III of the classification used in this paper, find an even higher survival rate than it shows, but all their cases have failed to react to a sanatorium régime first. Burrell and Fenton (32) have compared the results in 500 A.P. cases with the Midhurst, and find no difference between the two.

The Midhurst report does not deal with the working capacity of the survivors, so that it is not possible to use it as a standard for comparison with the A.P. material in this respect. Knight and Dublin (33), and Blyth Brooke (34), however, have published figures of this type. Although their material is not treated in quite the same way as the above A.P. material, a comparison will convey some impressions of value.

Percentages of Total Material Doing, or Fit for Full Work

	Group I.	Group II.	Group III.
A. P. material	93	79	36
Knight and Dublin	71	50	30
Blyth Brooke	37	29	14

Again, the discrepancy in favour of the A.P. material, especially in Groups I and II, is so great as to justify the impression that pneumothorax holds a better prospect of restoring working capacity than sanatorium treatment.

When the present series is considered with regard to symptoms, it is seen that in Group I 91 per cent., in Group II 76 per cent., and in Group III 32 per cent. of the total number of patients in each group have been rendered symptom-free, or are left only with a slight cough, and no, or scanty negative, sputum.

An Attempt to Assess the Value of Sanatorium Treatment in Conjunction with A.P.

A criticism of the material presented is that a large proportion of the cases have had sanatorium treatment in addition to artificial pneumothorax. It is now proposed to attempt to assess the influence of the sanatorium as an adjuvant, by separating the cases into those who went to a sanatorium and those who did not, to show to what extent these two divisions were qualitatively comparable, and then to compare them with reference to mortality, and the working capacity and symptoms of the survivors.

Of the 267 cases, 184 had sanatorium treatment as well as pneumothorax, and 83 had a pneumothorax only. The sex distribution was:

	Number.		Percentage.	
	Males.	Females.	Males.	Females.
Sanatorium + A.P.	94	90	51	49
A.P. only	45	38	54	46

and the distribution in clinical groups was:

	Number.			Percentage.		
	Group I.	Group II.	Group III.	Group I.	Group II.	Group III.
No sanatorium	21	33	29	25·3	39·9	34·8
Sanatorium	22	90	72	11·9	48·8	39·3

The percentage distribution in age groups was:

	No sanatorium.	Sanatorium.
–22	14·9	37·6
23–27	26·3	27·3
28–32	9·3	13·0
33–37	23·8	10·8
38–42	6·9	7·6
43–	18·8	3·7
	100·0	100·0

The number and percentage of sputum positives:

	Number.					
	No sanatorium.			Sanatorium.		
	Group I.	Group II.	Group III.	Group I.	Group II.	Group III.
T.B. positive	10	25	29	14	80	68
T.B. negative	11	8	—	8	10	4

	Percentage.					
	No sanatorium.			Sanatorium.		
	Group I.	Group II.	Group III.	Group I.	Group II.	Group III.
T.B. positive	47	75	100	63	89	95
T.B. negative	53	25	—	37	11	5

The state of the contralateral lung:

	No sanatorium.			Sanatorium.		
	Group I.	Group II.	Group III.	Group I.	Group II.	Group III.
Percentage not infected	76	43	10	70	43	10
Percentage suspicious	10	18	10	14	12	6
Percentage infected	14	39	80	16	45	84

The similarities disclosed in this table are maintained when inquiry is made into the number of zones infected and the type of disease.

A comparison of the observation period in the two divisions is best made by the accompanying graph (Fig. 4).

Thus the two divisions show a close parallelism in sex distribution, the state of the contralateral lung, and period of observation; the distribution in clinical groups is very similar except in Group I, where a greater proportion did not go to a sanatorium. In so far as the distribution in age groups is concerned, the group –22 is better represented in the 'sanatorium' division, but this is counterbalanced by a higher representation of the other age—mortality peak, 33–43—in the 'no-sanatorium' division. In positive

sputum incidence, Groups I and II are slightly higher in proportion in the sanatorium division. But when they are compared, the two divisions differ qualitatively only to an unimportant degree.

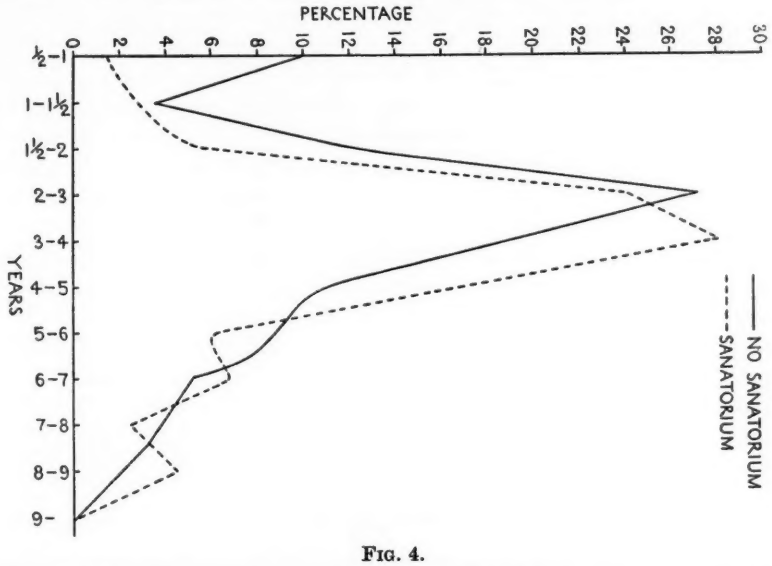

FIG. 4.

An analysis of the results in each of them has been made upon the lines already set forth:

Mortality: Number of Cases

	No sanatorium.			Sanatorium.		
	Group I.	Group II.	Group III.	Group I.	Group II.	Group III.
Untraced	2	1	3	—	1	—
Alive	18	25	13	22	83	37
Dead	1	7	13	—	6	35
	21	33	29	22	90	72

Mortality: Percentage of Cases

	No sanatorium.			Sanatorium.		
	Group I.	Group II.	Group III.	Group I.	Group II.	Group III.
Untraced	9·5	3	10	—	1	—
Alive	85·5	76	45	100	91	51
Dead	5·0	21	45	—	8	49
	100·0	100	100	100	100	100

If the 'untraced', of whose death there is no evidence from the Registrar-General's records, and the single Group I case, killed in an accident, are excluded from the experience, the percentage mortality is:

	No sanatorium.			Sanatorium.		
	Group I.	Group II.	Group III.	Group I.	Group II.	Group III.
Alive	100	78	50	100	93	51
Dead	—	22	50	—	7	49

Thus the only significant difference between the two divisions is one of 15 per cent. in Group II.

Rate of Mortality: Both Sexes and All Groups

No sanatorium.			Duration.	Sanatorium.		
Exposed to risk.	Deaths.	Rate of mortality.		Exposed to risk.	Deaths.	Rate of mortality.
78	4	—	0	182	2	—
73	4	—	1	180	15	—
55	6	—	2	142	9	—
35	4	—	3	94	8	—
21	1	—	4	51	6	—
17	1	—	5	29	1	—
7	1	—	6	18	—	—
4	—	—	7	13	—	—
—	—	—	8	3	—	—
—	—	—	9	—	—	—
290	21	0·072		712	41	0·058

	Males.				Females.		
	Exposed to risk.	Deaths.	Rate of mortality.	Duration.	Exposed to risk.	Deaths.	Rate of mortality.
No sanatorium	164	10	0·061	0 to	126	11	0·087
Sanatorium	359	21	0·058	9	353	20	0·057

When the rates of mortality for the combined sexes and groups are considered, that for the 'no sanatorium' is slightly higher; when the sexes are separated, that for males is almost identical in the two divisions, but for females the rate in the 'sanatorium' is appreciably lower.

Working Capacity of Survivors (Percentages)

	No sanatorium.			Sanatorium.		
	Group I.	Group II.	Group III.	Group I.	Group II.	Group III.
At full work	100	92	46	82	75	60
Fit for full work (unable to find it or non-workers)	—	4	31	18	13	10
Unfit for work	—	4	23	—	6	—
Instit. inmates	—	—	—	—	6	30

If the percentage of patients at full work is added to those who are fit for it, the differences in the two divisions are insignificant.

Symptoms of Survivors (Percentages)

	No sanatorium.			Sanatorium.		
	Group I.	Group II.	Group III.	Group I.	Group II.	Group III.
Symptom-free	95	68	62	87	72	62
Sl. cough and no or negative sputum	5	20	—	13	14	19
Sl. cough and pos. sput. No toxaemia	—	8	23	—	11	5
Considerable symptoms	—	4	15	—	3	14

The only considerable difference is that the sanatorium Group III shows a higher percentage of cases left with only a slight cough and negative sputum, and a smaller of those with a cough and positive sputum.

To summarize, the percentage mortality in Groups I and III is strikingly similar in the two divisions of the material; in Group II the 'sanatorium' shows an improvement of 15 per cent. on the 'no sanatorium' figure. The aggregate rates of mortality closely approximate to each other in the two divisions, but where the sexes are separated, whilst the rate for males is almost the same, that for females is 33 per cent. less in the 'sanatorium' division. In the working capacity and symptoms of the survivors the two divisions show a striking alikeness.

It would seem proper to conclude that within the limits of this small analysis, the influence of sanatorium treatment as an accessory to pneumothorax is not of primary importance; but the sanatorium must remain of considerable educational value.

It is possible to make some additional inferences of practical value with regard to the indications of pneumothorax therapy from the data set forth.

	Percentage mortality.		Percentage of survivors doing, or fit for, full work.		Percentage of survivors with no, or minimal, symptoms.	
	Males.	Females.	Males.	Females.	Males.	Females.
Group I	—	—	100	100	95	100
Group II	10·3	10·9	90	89	86	87
Group III	46·9	48·0	69	74	61	70

It is a truism of pulmonary tuberculosis that the earlier the disease is treated, the greater the chance of a successful issue. The above table, a summary of the results observed in this experience, demonstrates the difference between the chances of success in the early and moderately advanced patient and in the far advanced. If a case has been made out for the superiority of artificial pneumothorax over sanatorium therapy, then on humane, social, economic, and public health grounds, artificial pneumothorax in the individual patient should be undertaken earlier.

Though this attitude has its supporters (Morriston Davies (35), Bernard (36), Dumarest and Brette (11)), much opinion is opposed to it. Its grounds of opposition are mainly two; the more important is that the patient should be allowed a chance to 'beat the disease' himself, by a period of sanatorium treatment. How much of a chance he has is only too disappointingly shown by the results published from sanatoria. The general conclusion of the Midhurst report was 'something more is needed'. Moreover, according to modern conceptions of the pathogenesis of adult pulmonary tuberculosis, to collapse the lung of a patient is not to deprive him of the antigen, which allows him to build up his immunity again; but whilst this raising of immunity must be of primary importance in the principles upon which therapeutic effort is based, almost as much importance must be attached to preventing spread of infection to other areas of lung; this can only be achieved with some degree of certainty by collapse therapy.

The second ground of opposition is that artificial pneumothorax exposes the patient to a new, and probably unnecessary, set of dangers. How false this is, a glance at the table showing the percentage incidence of complications encountered in this experience will show. Small as this danger is, it must be noticed that it increases with the severity of the disease at the time of initiation of treatment, a fact undoubtedly connected with the greater occurrence of adhesions as the degree of disease progresses. This can only constitute another point in favour of the plea for earlier pneumothorax.

Summary

A series of 267 cases of pulmonary tuberculosis treated by artificial pneumothorax at an out-patient clinic of the Brompton Hospital during 1922–32 is compared qualitatively with the material which formed the substance of the Medical Research Council Special Report. What differences there exist between them are prognostically unfavourable in the present series.

Percentages and rates of mortality are compared in the present and the sanatorium cases. Amongst the early cases there was no mortality, as opposed to one of 23·1 per cent. for males and 13·5 per cent. for females in the sanatorium experience; in the moderately advanced, the mortality is 10·3 and 10·9 per cent. respectively for males and females in the present series, against 45·3 and 42·7 per cent. in the sanatorium; in the far advanced, the mortality reaches 46·9 per cent. for males and 48·0 per cent. for females in the present series, but is 74·4 and 67·6 per cent. respectively in the sanatorium. When a comparison is made, using the rate of mortality as a basis, the wide dissimilarity between the two experiences again becomes apparent.

Further information about the working capacity and residual symptoms of the survivors is given; in Group I 93 per cent., in Group II 79 per cent., and in Group III 36 per cent. of the total number of cases originally assigned to each group, are doing, or are fit for, full work; whilst 91, 76, and 32 per cent. respectively are free from symptoms or have only a slight cough and negative sputum.

184 cases went to a sanatorium after the induction of pneumothorax, and 83 were treated by pneumothorax alone. The percentage mortality is almost identical in Groups I and III, but in Group II the 'A.P.+ sanatorium' class shows a slightly smaller one. The aggregate rates of mortality in the two classes are very similar; but when the sexes are separated, the rate for females treated by the combined methods is lower than that for those treated by pneumothorax alone. As to the working capacity and the residual symptoms of the survivors, the differences between the two classes are insignificant.

Because an analysis of the cases shows clearly that the mortality varies directly, and the ultimate working capacity and residual symptoms inversely, with the degree and severity of disease at the inception of treatment,

it is suggested that a pneumothorax should be induced, in an earlier type of case than the conventional.

I must thank Dr. Batty Shaw for his kindness in putting this material at my disposal, Miss Marx and her staff for the excellence of their 'follow-up' system, without which this paper could not have been written, and finally my friend Brian Harley for the assistance he has given me with the actuarial tables and his helpful criticism of the paper as a whole.

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A COMPARISON BETWEEN THE BENDIEN CHEMICAL TEST AND SEDIMENTATION-RATE TEST IN THE PROGNOSIS OF TUBERCULOSIS [1]

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Introductory

In a previous publication one of us (J. F.) (1) formed the conclusion—based on the examination of 100 cases—that though the Bendien chemical test possessed little value in diagnosis, it appeared likely to be of use as a prognostic test since the results varied according to the type of cases examined, in the same way as the results of a sedimentation test might vary. Bendien (2) himself claims that his test is a superior prognostic test to the sedimentation rate, but does not offer convincing data in support of this claim.

It appeared to us desirable to investigate this claim, for even if the Bendien test were proved to be as reliable as—but no more reliable than—the sedimentation test, the former still possessed certain advantages of convenience over the latter. It is a serum test, and the serum can be used a few days after it is obtained from the patient without affecting the result. Moreover, the serum can be transmitted (by post or messenger) to a laboratory. The sedimentation test, on the other hand, ties one to the patient and to the clock in a manner that must definitely limit its application.

The investigation consisted in blood examinations of thirty-six patients, most of them at fortnightly intervals over a period of five months. One of us (J. F.) carried out the Bendien tests, while the other (D. M. D.) was responsible for the sedimentation tests and for the clinical observations.

Technique of the Bendien Chemical Test adopted

The original Bendien technique was departed from considerably, being inconvenient for clinical purposes. The following was briefly the routine adopted :—

1. Decinormal solutions of sodium vanadate and of acetic acid were prepared, and from these the Bendien reagents were made up. Only the first

[1] Received January 19, 1933.

ten of the twenty reagents were prepared, however; the remaining ten being found to have no significance in the test. Latterly only the first eight were used, after it had become clear that the ninth and tenth reagents could be safely omitted.

2. The actual test was carried out in small tubes of about 3 c.c. capacity, placed in racks accommodating about a dozen tubes in each row. A rack with four rows was found quite suitable, enabling four tests to be carried out simultaneously. By using several such racks it was possible to perform up to twenty tests at one sitting. The width of the tubes was not material so long as they were not too narrow to allow of thorough shaking of the contents.

3. Clear serum of the patient was obtained in the usual way, and 1 c.c. pipetted into a separate small tube to which 1 c.c. of distilled water had been added. The mixture was shaken, and 2 c.c. of the 50 per cent. serum was then added to each of the eight tubes.

1 c.c. of the sodium-vanadate-acetic acid reagent no. 1 was then added to tube 1, 1 c.c. of reagent no. 2 to tube 2, and so on for all the eight tubes.

Each tube was thoroughly shaken after the addition of each reagent. It is important not to leave the shaking of the mixtures to the end of the test, for precipitates invariably form (in all tubes) when the reagent is added to the serum. In normal serum the precipitate disappears on shaking in tubes 1 to 5, but if shaking is delayed the precipitates may not wholly redissolve.

4. The reading was obtained immediately the test had been completed, and was found to be practically the same as a twenty-four hour reading, the only difference being that the height of the precipitates immediately after they had formed was greater than their height twenty-four hours afterwards.

5. The result is best reported in the manner adopted by Bendien, who states the *number of the tube in which the precipitate first appears.* Frequently the result is by no means sharp, the end point appearing to lie between two tubes. Thus a reading 5–6 means that there is a turbidity but no definite precipitate in tube 5, while the precipitate is quite definite in tube 6.

When the precipitation commences in tube 1 the method advocated by Bendien becomes inadequate, as will be demonstrated in one of the charts below (Fig. 7). The degree of precipitation in tube 1 was shown to have a definite bearing on prognosis, and was worse with marked than with slight precipitation in that tube. The following method of report was finally adopted :—

1 for *slight* precipitation in tube 1.

1 a for *definite* precipitation in tube 1.

1 b for *complete* precipitation, the supernatant fluid being definitely turbid.

1 c for *complete* precipitation, supernatant fluid being perfectly clear.

Decinormal sodium vanadate. It would appear that the composition of crystalline sodium vanadate varies as regards the amount of water of

crystallization. Bendien adopted the formula Na_3VO_4, $10H_2O$. This I confirmed for a sample supplied by the British Drug Houses. Smith and Marrack (3), however (1931), obtained the formula Na_3Vo_4, $9H_2O$, while Freeman and others (4) obtained 11 molecules water of crystallization.

In view of this variability of samples it is essential that, if the results of different workers are to be comparable, the composition of the salt should be ascertained before making a decinormal solution. A standard solution of the $9H_2O$ is 10 per cent. stronger in actual Na_3VO_4 than the same solution of an $11H_2O$ salt.

The water content of the salt is readily obtained by heating in a hot oven at 160° C. a weighed sample in a platinum crucible until the weight is constant.

Technique of the Sedimentation Test adopted (5)

A mixture of one part of 3·8 per cent. sodium citrate and four parts of blood was obtained by drawing 1 c.c. of citrate solution into a 5 c.c. syringe and then filling with blood from the vein up to the 5 c.c. mark.

The contents of the syringe were emptied into a test-tube, thoroughly mixed, and sucked up into a 1 c.c. pipette graduated in hundredths of a c.c.: the pipette with the fluid level at 1 c.c. was then placed in a special stand and the level of the cell column read off after two hours. When only a small amount of sedimentation occurred, the column was found to have fallen only 0·1 to 0·2 c.c. at the end of two hours, giving readings of 0·9 to 0·8. When, however, sedimentation was marked, the cell column was found to fall 0·5 or even 0·7 c.c. in that time, giving readings of 0·4 to 0·3.

Survey of Results

151 Bendien tests were carried out, most of them simultaneously with a sedimentation test. The thirty-six cases were chosen so as to present all grades of severity of pulmonary tuberculosis, and in most of them the blood was examined on five to ten occasions.

The following table summarizes the results obtained in the first twenty-one cases.

A scrutiny of the results reveals a very high degree of correspondence between (1) the Bendien and the sedimentation tests, (2) the clinical course and the prognosis on the one hand, and the prognostic tests on the other.

Correlation between clinical prognosis and the prognostic tests. With only one exception (Case 19) in the whole series of cases the correlation between prognosis and the result of the tests was good, a bad prognosis being associated with a Bendien result of 1 or less, and a good prognosis being associated with a result of 4 or more. In Case 19 a clinically good prognosis was associated with a Bendien result 1. Nevertheless, there was a slight loss in weight over the observed period, while the final sedimentation rate

TABLE I. *Giving for each Case the Results of Consecutive Tests, with Notes on the Clinical Condition During the Period of Examination, and the Prognosis at the Time of the Last Test*

Case.		Results of prognostic tests [B = Bendien S = Sedimentation]										Clinical condition. Initial.	Intermediate	Final.	Prognosis.
1	B	1	3	2	4	4	4	5	4	—	—	L_2S	Improvement	L_2s	Moderately good
	S	0·6	0·64	0·62	0·78	0·82	0·78	—	0·82	—	—				
2	B	1	1 a	1	1 a	1 b	1 a	1 ab	1 a	1 a	1 a	L_3S	Slight improvement	L_3S	Ultimately bad
	S	0·52	0·5	0·6	0·58	0·54	0·62	—	0·6	—	—				
3	B	6	—	6	4	4	4	5	7	4·5	—	L_3	Unchanged	L_3	Good
	S	0·78	—	0·8	0·74	0·76	0·78	—	0·82	0·8	—				
4	B	1–2	—	2–3	1–2	1 a	1	1	—	—	—	L_3S + larynx	Unchanged	Going downhill	Bad
	S	0·5	—	0·58	—	0·46	0·48	—	—	—	—				
5	B	1 c	—	—	—	—	—	—	—	—	—	L_3S + larynx + intestine	Death	—	—
	S	0·3	—	—	—	—	—	—	—	—	—				
6	B	4	4	5	5	5	—	—	—	—	—	L_2s	L_2	L_1	Good
	S	0·8	0·84	0·88	0·82	0·86	—	—	—	—	—				
7	B	4	5	6	6	6	—	—	—	—	—	L_1s	Improvement	L_1	Good
	S	0·82	0·84	—	0·84	0·9	—	—	—	—	—				
8	B	2	4	4	4	6	—	—	—	—	—	L_2s	L_2	L_1	Good
	S	0·74	—	0·9	0·9	0·82	—	—	—	—	—				
9	B	4	3–4	3	4	—	—	—	—	—	—	L_2	Unchanged	L_2	Good
	S	0·8	—	0·72	0·78	—	—	—	—	—	—				
10	S	2	1 a	1–2	—	—	—	1 b	—	—	1	L_3S + larynx	Worse	Going downhill	Bad
	B	0·64	0·54	0·6	—	—	—	0·5	—	—	0·52				
11	B	1	1–2	4	4	4	4	4–5	—	—	4	L_3S	Improvement	L_3s	Immediate good Ultimate bad
	S	0·58	0·68	0·72	—	0·7	0·74	0·76	—	—	—				
12	B	1	1–2	1	2	2–3	2	—	—	—	1 c	L_3S	L_3s	L_3S + kidney	Bad
	S	0·6	0·62	0·62	0·68	—	0·68	—	—	—	0·4				

13	B	2	2–3	2–3	1	2	4	4	—	—	—	L_3S	Improvement	L_3s	Immediate good
	S	0·56	0·58	0·6	0·6	0·7	0·78	—	—	—	—				Ultimate bad
14	B	1 b	1	1 a	1–2	1 b	1 a	1–1	—	—	1 ab	L_3S	Improvement	L_3s	Immediate good
	S	0·48	0·5	0·46	0·6	0·6	—	0·6	—	—	—				Ultimate bad
15	B	1 c	1 b	1 b	1 b	1 c	1 c	1 b	—	—	—	L_3S	Unchanged	Worse	Bad
	S	0·5	0·56	0·58	—	0·46	—	0·54	—	—	—				
16	B	2	4	4	—	—	4	5	5	—	—	L_2s	Improvement	L_2	Good
	S	0·7	0·72	0·8	—	0·86	0·82	0·86	—	—	—				
17	B	2	4	4	4	4–5	2	4–5	—	—	—	L_2S	Improved then had febrile attack	L_2s	Moderately good
	S	0·7	0·8	0·78	—	0·8	0·76	0·82	—	—	—				
18	B	4	5	5	—	—	—	—	—	—	—	L_1s + pleural effusion	Effusion subsided	L_1	Good
	S	0·8	0·9	0·92	—	—	—	—	—	—	—				
19	B	2	4	4	—	—	4	1	—	—	—	L_3s	Unchanged	L_3s	Immediate good
	S	0·84	0·9	0·88	—	—	—	0·82	—	—	—				Ultimate bad
20	B	3–4	2	3–4	4	5	—	5	—	—	—	L_3s	Improvement	L_3	Good
	S	0·7	0·68	0·76	0·74	0·82	—	0·84	—	—	—				
21	B	1 a	1 b	1 b	1 c	1 ab	1 bc	—	—	—	—	L_3s	L_3S	Going downhill	Bad
	S	0·5	0·46	0·5	—	0·54	0·46	—	—	—	—				
22	B	—	1 c	—	—	—	—	—	—	—	—	T.B. peritonitis amyloid kidney	Going downhill	Death	—
	S	0·25	0·25	0·22	—	—	—	—	—	—	—				

The symbol L represents the local lung lesion. The figure underneath it represents its extent, according to the Turban-Gerhardt classification.

The symbol S represents the systemic disturbance. If a capital S is used, the systemic disturbance is considerable, while a small s indicates only a slight degree of toxaemia.

Thus L_3s represents a gross anatomical lesion, with slight systemic disturbance.

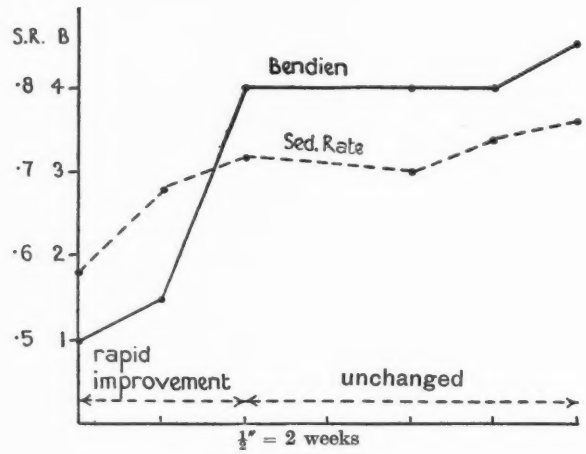


FIG. 1 (Case 11).

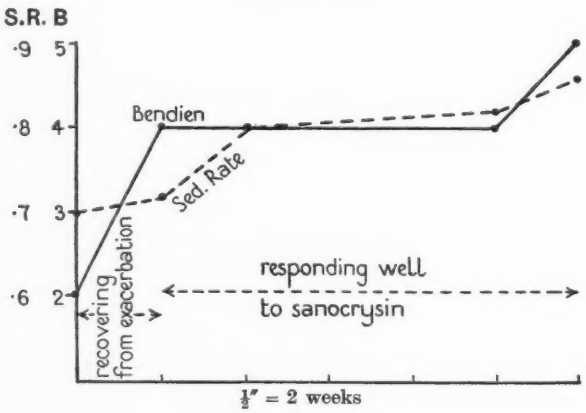


FIG. 2 (Case 16).

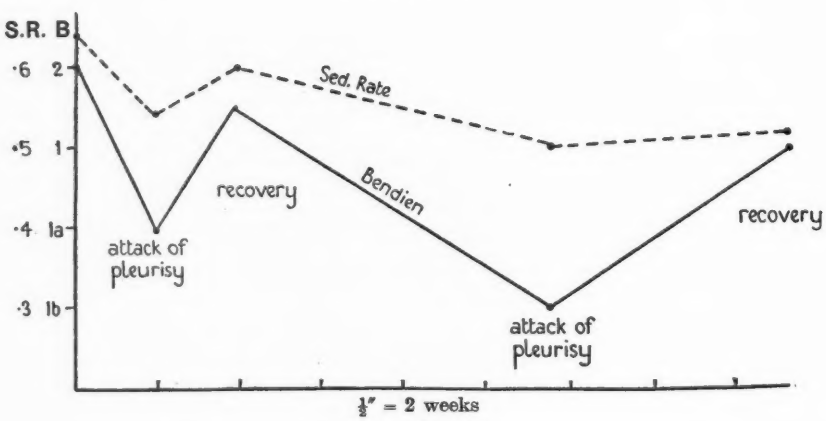


FIG. 3 (Case 10).

agreed with the Bendien result in being the lowest for the whole period; it was therefore possible that the clinical condition of the patient was not a true expression of the activity of the process.

Correlation between the clinical course during the observed period and the prognostic tests. From Table I it is clear that in the main the clinical course is faithfully reflected in the variations of the prognostic tests. (See Figs. 1, 2, being charts of Cases 11 and 16 respectively.)

It will be noticed, however, that whereas definite clinical incidents such as occurred in Cases 10 (Fig. 3), 13 (Fig. 4), and 17 (Fig. 5) are definitely reflected in the Bendien and the sedimentation curves, there are in addition frequent fluctuations in these curves without clinical incidents to account for them. Cases 4 (Fig. 6), 15 (Fig. 7), and 20 (Fig. 8) are examples.

It is possible that these fluctuations in the tests, without clinical variations to account for them, possess definite significance, and point to an increase in the activity of the disease, or to improvement, so slight as not to be mirrored in the clinical picture.

Statistical Analysis

The correlation coefficient between the Bendien and the sedimentation tests was calculated in the usual way, a correlation table and frequency-distribution tables being first prepared. For the purposes of calculation, the Bendien results 1 a, 1 b, and 1 c were replaced by 0, −1, and −2 respectively.

The result obtained was $r = 0{\cdot}8066 \pm 0{\cdot}033$.

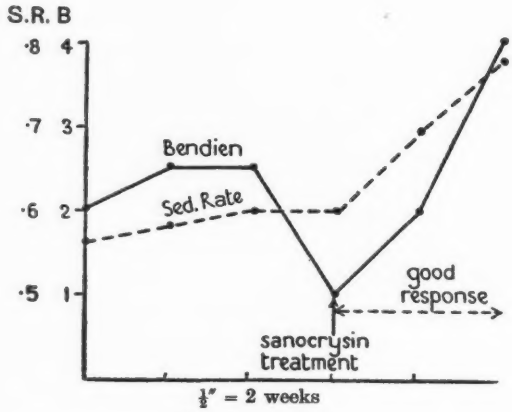
This high degree of correlation was further reflected in the regression curve shown in Fig. 9. The points on this curve between 1 c and 5 (with the exception of the second point) lie practically in a straight line, from which the following conclusions might be made:—

1. That the Bendien results up to 5 are a function of the sedimentation rate.

2. That the Bendien results above 5 are not associated with a corresponding rise in the sedimentation rate and therefore are not correlated with the latter.

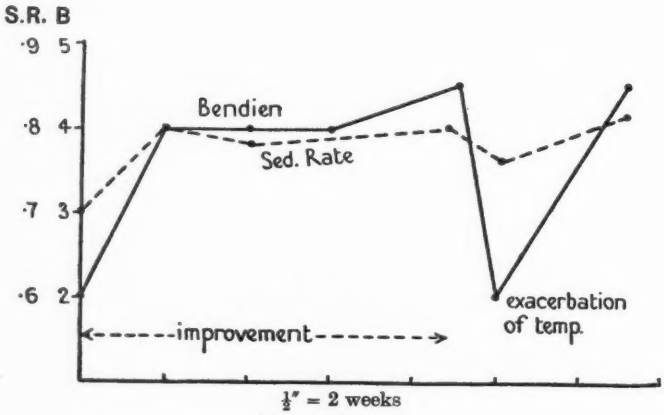
3. That the Bendien results 1 a and 1 b (i.e. 'definite' and 'complete' precipitation in tube 1) do not differ in their interpretation, since they correspond to practically the same sedimentation rate. A result 1 c nevertheless is two units below 1 a.

4. The regression coefficient of the sedimentation rate in relation to the Bendien test $= r\frac{\sigma_s}{\sigma_B} = 0{\cdot}8066\frac{0{\cdot}1489}{2{\cdot}267} = 0{\cdot}053$. This suggests that there is a rise of 0·053 in the sedimentation rate of every rise of 1 in the Bendien test. Actually, since the curve is flat above the Bendien value 5, the regression coefficient for the portion of the curve below this value is higher, i.e. 0·07.



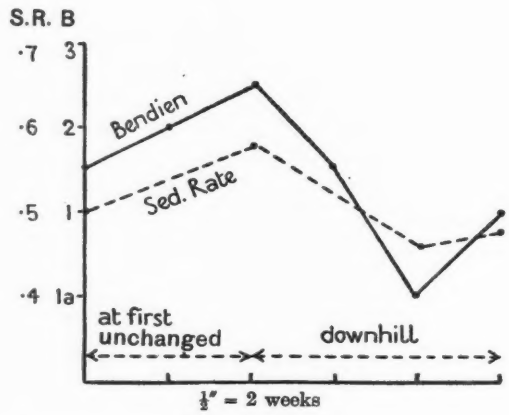
½″ = 2 weeks

FIG. 4 (Case 13).



½″ = 2 weeks

FIG. 5 (Case 17).



½″ = 2 weeks

FIG. 6 (Case 4).

Hence, for the portion of the curve where the sedimentation rate and the Bendien tests are truly correlated, a change in the sedimentation rate of 0·07 corresponds to a change in the Bendien result of 1.

The degree of correspondence between the two tests was investigated from another standpoint. An analysis was made of the Bendien and sedimentation charts of each patient so as to show

1. The total number of steps in each chart (a step being the line joining two consecutive points).

2. The number of times the corresponding steps of the charts changed in the same manner, i.e. both rose, fell, or showed no change (= agreement).

3. The number of times a Bendien result changed while the corresponding sedimentation rate remained unchanged (= no disagreement).

4. The number of times a sedimentation rate changed while the Bendien test remained unchanged (= no disagreement).

5. The number of times the results changed in opposite directions (= disagreement).

The results are summarized in the table below.

TABLE II

S.	B.	No. of steps.		
+	+	35	Agreement	= 55
—	—	20		
+	0	16	Sedimentation changing, Bendien same	= 21
—	0	5		
0	+	2	Bendien changing, Sedimentation same	= 5
0	—	3		
—	+	2	Frank disagreement	= 2
			Total	83

S = sedimentation rate B = Bendien result + = rise — = fall 0 = no change

Analysis of Table II. Hence, in a total of 83 steps derived from the first twenty-one cases, there was

1. Frank disagreement in only two instances = 2·4 per cent.

2. A change in one test but not in the other in twenty-six instances = 31·3 per cent.

3. Complete agreement in fifty-five instances = 66·3 per cent..

In the two cases of disagreement the difference was negligible in one case (Case 20), the changes in both tests being slight and probably within range of error. In the second instance disagreement was marked (Case 8, Fig. 10), but the clinical evidence bore out the Bendien test rather than the sedimentation rate.

Of the large percentage (about 30 per cent.) of results in which only one test showed a change, it is very significant that most of them (twenty-one instances out of twenty-six) *showed a change in the S. R. but not in the Bendien.*

It is to be inferred from this that a change in the Bendien result is *more significant* than a change in the S. R. It is probable that the cause of this is not necessarily a greater reliability, but rather a lesser sensitiveness of the Bendien test. Obviously, transition from a Bendien result 4 to a result 3

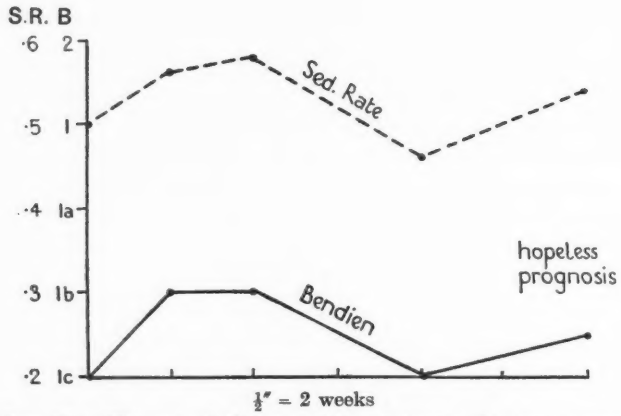


FIG. 7 (Case 15). The remarkable parallelism between the two curves would not have appeared if the Bendien method of reading had been adopted (i.e. 1 for precipitation in 1st tube, without recognizing degree of precipitation.)

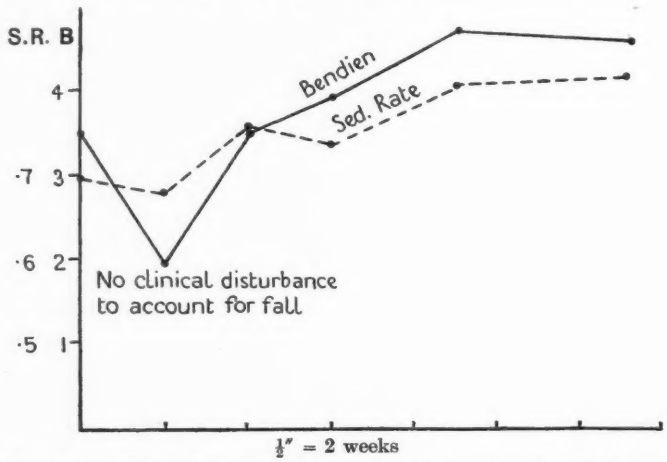


FIG. 8 (Case 20). Note slight disagreement between tests at 3rd step.

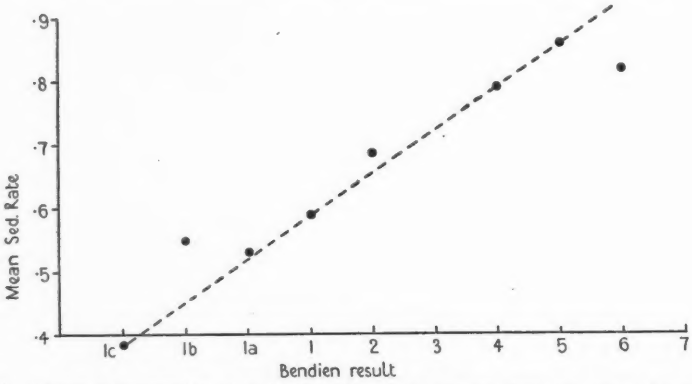


FIG. 9. Curve of regression of sedimentation-rate test on Bendien test. Regression coefficient = 0.07.

will not be observed until precipitation in tube 3 is sufficiently gross to be detectable. Hence intermediate values cannot be determined, although the result 3–4 indicates generally a value intermediate between 3 and 4.

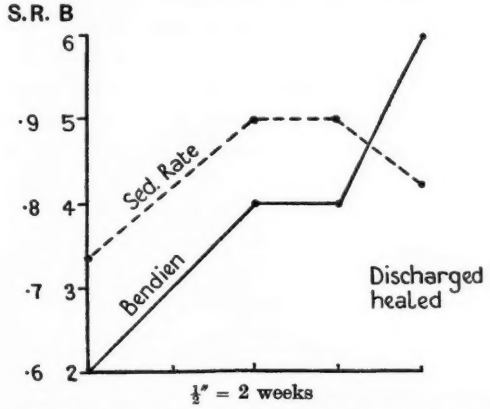


FIG. 10 (Case 8). This is the only case showing definite contradiction between tests (3rd step). Initial agreement is very close. Clinically the Bendien result is upheld.

Correlation Coefficient between Degree of Pyrexia in Pulmonary Tuberculosis and Bendien Result

This was calculated from data given in tables in Bendien's book (pp. 28, 29), in which both temperature and Bendien result are given (fifty-five cases). The correlation coefficient was calculated and found to be $-0{\cdot}823 \pm 0{\cdot}043$.

High as this degree of correlation is, there is little doubt that the correlation between the Bendien result and the activity of the tuberculosis lesion is even higher still, since the temperature is not necessarily a faithful index of activity. Many of our own advanced cases, for example, were persistently apyrexial.

It is difficult actually to estimate the correlation between the Bendien result and the activity of the pathological process, since none of the clinical signs or symptoms (e.g. temperature, pulse, weight, T.B. in sputum) that could be chosen for comparison with the test are, taken alone, satisfactory expressions of activity.

Reasons for Parallelism and for Deviations from Parallelism between S. R. and the B. Test

The conclusion is inevitable that the parallelism between the two tests is due to a common mechanism—namely, the absorption of necrotic material formed in proportion to the activity of the lesion. This leads to an alteration in the protein balance of the blood manifesting itself physically in the relative increase in sp. gr. of the R.B.Cs. (sedimentation rate increased), and chemically by displacement to the left in the Bendien test.

It is highly probable, however, that the chemical factors causing an

increased sedimentation rate are not identical with those causing displacement to the left in the Bendien test—otherwise the parallelism between the tests would be complete or within the limits of experimental error.

In view of the frequent lack of parallelism between the two tests (i.e. a large change in one test being associated with little or no change in the other), it must be inferred that the chemical factors (no doubt chiefly protein in nature) responsible for the two tests are either distinct, but highly correlated in view of their common origin from necrotic material; or else they overlap, certain proteins influencing both tests, others influencing either one test or the other.

The latter hypothesis is more probable, and conforms to the views generally held as to the mechanism of the tests. An increase in fibrinogen and globulin in plasma is held to account for an increased S. R., while a relative increase in globulin is Bendien's explanation of a displacement to the left.

Conclusions

1. The Bendien test is closely correlated with the sedimentation rate, both being useful indices of activity in pulmonary tuberculosis.

2. While there is no reason to believe the Bendien test either more or less accurate than the sedimentation rate, it has the following advantages:—

   (*a*) It is a serum test, and therefore more convenient.

   (*b*) It does not show so readily minor fluctuations, and therefore its variations are more significant.

It has the disadvantage of requiring two very accurately prepared reagents. In the preparation of the acetic acid solution an error of $N/10 \times (\pm 0{\cdot}005)$ causes a displacement in the result by 1 tube. The sodium vanadate varies in the amount of water of crystallization, and the decinormal solution can therefore be safely prepared only by obtaining the weight of the anhydrous salt.

3. The Bendien chemical test is a useful prognostic test in pulmonary tuberculosis, and probably in other conditions where the sedimentation rate has been found useful. It may safely be adopted as an alternative prognostic test where the S. R. is impracticable.

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PATHOLOGICAL CHANGES IN THE CAROTID SINUS AND THEIR RELATION TO HYPERTENSION[1]

By C. A. KEELE

(From the Departments of Pathology and Physiology of the Middlesex Hospital)

Recent physiological investigation has shown that the afferent nerves from the carotid sinuses and the arch of the aorta (Blutdruckzügler, buffer nerves), play an essential part in the regulation of the normal blood-pressure (Hering (1), Heymans (2), Koch (3), Wright (4)). These nerves normally exercise a tonic inhibitory influence in animals, and following their complete removal in acute experiments marked hypertension results. A number of observers (Koch, Mies, and Nordmann (5), Heymans (2), Wright, Kremer, and Scarff (6)) have further shown that if the sinus and aortic nerves are removed in stages and the animals allowed to survive, a marked chronic arterial hypertension may result, associated in the rabbit with medial degeneration and calcification, especially in the aortic arch. Speculation has taken place whether the buffer nerves are ever put out of action in the human subject and thus lead to the development of hypertension. Hering has definitely suggested that atheromatous changes in the aorta and sinuses, leading to hardening of the intima and media, might prevent the transmission of the internal blood-pressure changes to the sensory nerve-endings in the adventitia, and these endings would consequently cease to function. On this theory there need be no degeneration or alteration of the nerve-fibres themselves, and there is evidence that in atheroma of the sinuses the nerve-endings are normal on histological examination (Sunder-Plassman (7)), and respond very readily to external pressure (Hering (1)). But, as has been pointed out, with a hardened media and an intact adventitia, the nerve-endings may be very sensitive to compression from without, and yet respond in a lessened degree to endosinusal pressure changes. Regniers (8) claims that in six cases of hypertension occlusion of the common carotid artery (with subsequent lowering of endosinusal pressure) did not produce the usual tachycardia, and only raised the blood-pressure to a small extent; disocclusion did not produce the usual slowing of the heart.

[1] Received December 17, 1932.

Goormaghtigh (9) investigated the sinuses and aorta in thirty cases dying of various conditions. He found that those with the greatest heart weight (no clinical data were available), showed greater changes in the sinuses and aorta. Hasselbach (10) studied seventy-two cases, of which nineteen were probably or possibly instances of hypertension. He found on the contrary no definite association between the degree of sinus involvement and the level of the blood-pressure.

In this paper an attempt has been made by the correlation of pathological and clinical data to throw further light on this subject.

Material and Methods

The material on which this paper is based consisted of fifty-five consecutive and unselected cases that came to post-mortem examination. The age incidence of the series was from 7 to 79 years. A careful study was made of the condition of the arch of the aorta, the bifurcations of the innominate common carotid and common iliac arteries, and special attention was paid to the carotid sinuses. An attempt was made to represent the degree of atheromatous degeneration present at any particular site on macroscopic examination by means of the figures 1, 2, 3, and 4 which were given the following significance: 1, represents slight fatty flecking; 2, marked fatty flecking; 3, slight calcification present also; 4, marked calcification present. In the case of the carotid sinuses the approximate extent of the lesion was recorded, the figures i, ii, iii, and iv being used according to whether $\frac{1}{4}$, $\frac{1}{2}$, $\frac{3}{4}$, or the whole of the sinus was involved in the atheromatous process. In twenty cases histological examination of the sinuses was carried out, but this added little to the results obtained macroscopically. The blood-pressure in life was known in thirty out of the fifty-five cases. The weight of the heart was noted in all. Five of the cases examined had shown definite and marked hypertension during life. Three others showed *post mortem* marked cardiac enlargement, mainly affecting the left ventricle, without any evidence of valvular disease. Although the blood-pressure in these latter cases during life was within normal limits, they were almost certainly instances of essential hypertension in which the blood-pressure had been lowered because of the development of congestive heart failure from which they died. Cases in which the blood-pressure was only slightly raised or with slightly excessive heart weight were not included as instances of hypertension.

Results

The results obtained in the cases with clinically recorded blood-pressure are set out in summary form in Tables I, II, and III, but all the cases have been considered in the analysis.

Changes in the carotid arteries and sinuses. Atheromatous changes are of very frequent occurrence in the carotid sinuses and were noted in fifty of the fifty-five cases examined. The lower part of the sinus was more

markedly affected than the upper. The bifurcation angle was also frequently involved. The common carotid artery was involved less frequently than the sinuses, and showed the most definite changes in its upper part just below the point of bifurcation. The internal carotid artery was never found affected to the slightest degree, and the external carotid only rarely so at the points of origin of its branches.

Relation of carotid sinus changes to age. In thirty-two instances the degree of change in the carotid sinuses was of the order 1 and 2. The average age of this group was 45 years and the range 16 to 79 years. In nearly all of these the flecking was of a patchy character, thus differing from the linear flecking which is characteristic of the upper part of the common carotid artery (Beneke (11)). In the eighteen cases in which the sinuses were affected to the degree 3 and 4 the average age was 62 years and the range 42 to 76 years. It is clear from these figures that the degree of change in the sinuses is closely related to age.

Relation of changes in carotid sinuses to those in aorta and at chief bifurcations. The arch of the aorta was as frequently involved as the sinuses. Only rarely are changes present in one and absent in the other. In this series the sinuses were involved alone in three instances and the aorta alone in three instances. The common iliac bifurcation was affected about as often as the sinuses and the innominate bifurcation slightly less frequently. Atheromatous change in the sinuses is thus part of a widespread involvement of the main arteries.

Relation of changes in carotid sinuses to hypertension. Among the eighteen cases with marked sinus involvement (degrees 3 and 4) there were only two instances of hypertension. No. 25 (aged 58) had a blood-pressure during life of 215/130; No. 38 (aged 34), whose heart weight was 27 oz. and who showed marked left ventricular hypertrophy, was almost certainly a case of old hypertension, though the blood-pressure recorded was 125/90. The remaining sixteen cases showed normal blood-pressure and heart weight and could not reasonably be regarded as instances of hypertension.

Among the thirty-two cases with slight involvement of the carotid sinus (degrees 1 and 2) there were four instances of hypertension—three of the 'essential' type (Nos. 36, 45, and 54), one of renal origin (No. 49). In the last case the atheromatous changes were very slight indeed.

In addition there were two cases with increased heart weight and no valvular lesion in whom the diagnosis of hypertension was practically certain in spite of a normal blood-pressure in life. These findings indicate that there is no obvious causal relationship between atheroma of the sinuses and hypertension.

Involvement of aorta and sinuses in hypertension. In only one instance of hypertension was the extent of involvement sufficient to make Hering's hypothesis at all possible. On the other hand there were eight cases (Nos. 16, 18, 28, 30, 35, 39, 44, and 55) in whom changes were equally marked, but in whom there was no definite evidence of hypertension.

Discussion

The above findings are in agreement with those of Hasselbach (10), and suggest that in the human subject it is improbable that hypertension is produced through atheromatous involvement of the aorta and carotid sinuses. Goormaghtigh (personal communication) has recently come to a similar conclusion. The clinical evidence that in hypertension the sinus nerve-endings are not functioning is by no means conclusive. Experimentally, Okuneff (11) found that after atheromatous changes had been induced in the aorta (of the rabbit) the aortic nerves were still transmitting tonic inhibitory impulses. Further, it is not definitely known that in life atheromatous calcification is as hard as it is *post mortem* (MacCordick (12)). As the buffer nerves function vicariously one for the other, their destruction would have to be fairly complete before marked hypertension could result, and the atheromatous lesion would have to be correspondingly marked and extensive.

Conclusions and Summary

1. The possibility that clinical hypertension might be due to atheromatous changes in the carotid sinuses and the aorta, putting out of action the tonic inhibitory buffer nerves, was studied pathologically in fifty-five cases, of which eight were instances of hypertension.

2. No relationship could be established in this series between the degree of sinus and aortic involvement and presence of hypertension.

3. Atheroma of the carotid sinuses is very common, is mainly related to age, and is usually associated with a similar degree of involvement of the aortic arch, the innominate and common iliac bifurcations, and the upper end of the common carotid artery.

The author desires to express his thanks to Professor McIntosh of the Bland-Sutton Institute of Pathology for permission to make use of post-mortem material, to Dr. Scarff of the same department, and to Professor Wright of the Physiology Department for help and advice.

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TABLE I. *Cases of Hypertension*

Case.	Sex.	Age.	Carotid sinuses.	Common carotids.	Innominate bifurcation.	Aorta.	Iliac bifurcation.	B.P.	Wght. and hght.	Heart.	Diagnosis.
25	M	58	R 2 and 4 (iii)	4	4	4	4	215/130	104 lb. 6′ 2″	12 oz.; coronary atheroma; myocardial fibrosis.	Carcinoma of head of pancreas; hypertension.
36	M	69	1 (iii)	1	1	3 and 4	3	300/150	170 lb. 5′ 9″	15 oz.; no valvular lesion.	Hypertension; dissecting aneurysm of aorta.
45	M	57	1 (ii); 2 at bifurcation	2	—	3	—	200/125 B.P. + 5 yrs.	168 lb. 5′ 9″	18 oz.; left ventricle + no valvular lesion.	Perforated duodenal ulcer; hypertension.
49	F	21	L = 1—(i); R = 1— with small patch of 3	0	0	0	0	250/140	103 lb. 5′ 2″	13 oz.; left ventricle + no valvular lesion.	Uraemia; chronic Glomerulo-tubular nephritis.
54	F	45	9 (i)	1 and 2 above 0 below	4	2	4	170/135	86 lb. 5′ 2″	13 oz.; coronary disease; myocardial fibrosis.	Hypertension; congestive failure; no rheumatic disease.

TABLE II. *Cases with Increased Heart Weight and no Valvular Lesion. Normal Blood-pressure in Life, but almost certainly Cases of Old Hypertension*

Case.	Sex.	Age.	Carotid sinuses.	Common carotids.	Innominate bifurcation.	Aorta.	Iliac bifurcation.	B.P.	Wght. and hght.	Heart.	Diagnosis.
38	M	34	2 (i); 3 at bifurcation	1	3	3	3	125/90	154 lb. 5′ 10″	27 oz.; left ventricle + no valvular lesion.	Hypertensive cardiac failure.
42	M	33	1 (ii)	0	1	2	0	100/85	190 lb. 6′ 2″	23 oz.; left ventricle + tricuspid incompetence.	Hypertensive heart disease; cardiac failure.
43	M	51	R = 2 (ii) L = 1 (ii)	1 above, 0 below	1	3	One = 3 Other = 0	105/75	140 lb. 5′ 6″	20 oz.; mitral and tricuspid incompetence.	Hypertensive heart failure.

TABLE III. *Other Cases with Clinically Recorded B.P. Arranged in Order of Age*

Case.	Sex.	Age.	Carotid sinuses.	Common carotids.	Innominate bifurcation.	Aorta.	Iliac bifurcation.	B.P.	Wght. and hght.	Heart.	Diagnosis.
24	F	79	1 (iii)	4 upper ½ 2 lower ½	4	4	4	145/60	91 lb. 5′ 4″	9½ oz.; no valvular lesion.	Carcinoma of head of pancreas.
55	M	67	4 (ii) 2 (ii) = (iv)	2 above, 0 below	2	2	3	180/90	158 lb. 5′ 6″	13 oz.; coronary atheroma myocardial fibrosis.	Prostatectomy pyelitis.
9	M	66	Bifurcation = 3 Otherwise = 0	Bifurcation = 3 Otherwise = 0	1	3 and 4	3 and 4	175/90	127 lb. 5′ 5″	9 oz.; no valvular lesion.	Carcinoma of pharynx.
47	M	62	0	1 above, 0 below	—	3	2	130/75	139 lb. 5′ 8″	11 oz.; no valvular lesion.	Carcinoma of bladder.
27	F	57	0	1 at bifurcation	2	3	—	90/75	98 lb. 5′ 6″	11 oz.; no valvular lesion.	Carcinoma of stomach.
7	F	55	L = 1 (i) R = 2 (i)	Upper ½ L = 2 Upper ½ R = 1	2	3	—	145/100	130 lb. 4′ 10″	10 oz.; no valvular lesion.	Ac. pyelo-nephritic uraemia.
11	F	54	2 (i)	R = 1 above nil below	2	2	—	130/80	138 lb. 5′ 3″	7 oz.; no valvular lesion.	Carcinoma of rectum.
46	M	54	1 (i) lower sinus	—	—	2	2	150/100	182 lb. 5′ 10″	14 oz.; left ventricle + no valvular lesion.	Pyonephrosis.
37	M	50	1 (iii)	1	—	4	4	120/60	125 lb. 5′ 8″	10 oz.; no valvular lesion.	Mediastinal neoplasm.
10	M	42	1 (i)	L = 2 R = 2 upper ½ = 0 lower ½	—	3	1	120/65	160 lb. 6′ 0″	13 oz.; no valvular lesion.	Hodgkin's disease.

TABLE III (*continued*)

Case.	Sex.	Age.	Carotid sinuses.	Common carotids.	Innominate bifurcation.	Aorta.	Iliac bifurcation.	B.P.	Wght. and hght.	Heart.	Diagnosis.
16	F	42	R = 4 lower sinus 2 elsewhere (iii) L = 3 lower sinus 2 elsewhere (iii)	R = 2 upper ½ 0 lower ½ L = 2	2	3 and 4	4	130/80	116 lb. 5′ 7″	7 oz.; no valvular lesion.	Carcinoma ventriculi.
48	M	42	1 (i) lower sinus	1 above, 0 below	—	2	—	120/80	130 lb. 5′ 6″	10 oz.; no valvular lesion.	Aplastic anaemia.
23	F	40	R = 1 (ii) L = 1 and 2 (ii)	R = 3 in middle 2 above L = 1 upper ½	0	2	0	120/80	132 lb. —	12 oz.; no valvular lesion.	Cholecystitis.
12	F	39	1 (ii)	L = 1 above 0 below R = 1	1	1	1	135/90	138 lb. 5′ 8″	14 oz.; slight thickening of mitral and aortic valves.	Toxaemia of pregnancy; adherent pericardium.
20	F	33	0	1 at bifurcation	—	2	0	120/75	132 lb. 5′ 0″	8½ oz.; no valvular lesion.	Pyonephrosis.
3	F	31	2 (ii)	Upper ½ = 0 Lower ½ = 0	2	1	1	140/95	72 lb. 5′ 6″	5 oz.; no valvular lesion.	Carcinoma ventriculi.
26	M	31	1 (i)	0	0	0	0	110/80	144 lb. 5′ 6″	8 oz.; no valvular lesion.	Gastric ulcer and cirrhosis of liver.
41	F	27	1 (ii)	0	0	0	1 — on R 0 on L	115/75	90 lb. 5′ 7″	7 oz.; no valvular lesion.	Hodgkin's disease.
51	F	26	1 (ii)	0	0	2	L = 0 R = 1	130/80	93 lb. 5′ 7″	8 oz.; no valvular lesion.	Colitis (dysentery).
15	M	22	1 and 2 (i)	1	—	1	1 and 0	140/90	110 lb. 6′ 1″	12 oz.	Infective endocarditis.
22	F	16	R = 1 (i) L = 1 (ii)	R = 2, L = 1	3	3	—	135/60	124 lb. 5′ 6″	24 oz.	Rheumatic carditis; adherent pericardium; cardiac hypertrophy.

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THE ELECTROCARDIOGRAM IN SYPHILIS[1]

AN EXAMINATION OF 232 CASES OF SYPHILIS AND 156 CONTROLS

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With Plates 19 to 22

Carey Coombs (1) has recently made such an excellent review of the whole subject of cardiovascular syphilis in this journal, that our references to the work of other authors can be reduced to a minimum, and confined to observations on the electrocardiogram. Most investigations on cardiovascular syphilis have been made at heart clinics and deal with established cases of heart disease, whilst observations on cardiac changes in the course of syphilitic infection are comparatively few. Ingraham and Maynard (2) examined twenty-seven cases of syphilis and found no abnormalities in the electrocardiogram other than a high incidence of left ventricular preponderance. Turner and White (3) studied fifty cases of early syphilis, chiefly in the secondary stage, and were not able to find either clinical or electrocardiographic evidence sufficient to indicate myocardial disease. Arnett (4) seems to have made the most extensive researches into the question. He examined 205 women with tertiary syphilis, 25 with secondary syphilis, and 78 controls. His criteria of abnormality were:

Inverted, diphasic, or iso-electric T-waves in Leads I and II; *P-R* interval greater than 0·2 seconds; *Q. R. S.* exceeding 0·10 seconds or having an amplitude of 5 mm. or less. No account was taken of left ventricular preponderance.

His results show very few electrocardiographic defects. The *P-R* interval was prolonged in two cases, both in the tertiary group. The *Q. R. S.* was prolonged in one case only, a woman with tertiary syphilis but who also had chronic glomerulo-nephritis. T-wave defects were found in five cases of tertiary syphilis, and one control. It is to be noted, however, that the control patient was abnormal in having 'pelvic inflammation' and a raised blood-pressure.

Contrasting forcibly with these observations are those of Juster and Pardee (5), who electrocardiographed fifty cases presenting clinical signs of

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cardiovascular syphilis—namely, cases of aortitis, of whom two-thirds had aortic insufficiency. Of these, 85 per cent. showed abnormal T-waves, in 20 per cent. of the coronary type due to the extension of syphilitic aortitis to the coronary orifices.

The more frequent occurrence of abnormal electrocardiograms in patients complaining of cardiac symptoms than in those attending for other syphilitic manifestations is to be expected, and suggests that the incidence of cardiac syphilis can be more satisfactorily established by examining cases drawn from a venereal rather than a cardiac clinic.

Much confusion exists about the stage of syphilis at which the heart is attacked. Notable authorities describe cases of heart affections in the secondary stage, as in a case described by Vaquez (6) of a girl with secondary syphilis who developed a typical Stokes Adams' syndrome, presumably on a syphilitic basis. Similarly, Brooks (7) reported two cases of aneurysm developing within six months of the primary syphilitic lesion.

Other observers deny that invasion of the heart takes place in the early stages of syphilis except on rare occasions. Thus Cohn (8) says that 'syphilis rarely causes detectable cardiac damage in the primary or secondary stages', whilst Wilson, Wile, Wishart, and Hermann state 'that study of about sixty patients with primary or secondary syphilis has convinced us that reliable clinical or electrocardiographic evidence of involvement of the heart or aorta during this stage of the disease is decidedly rare'.

The present investigations were undertaken with the following objects: (i) To gain some idea of the incidence of myocardial damage in patients attending venereal clinics in whom heart disease was not obvious. (ii) To see whether the electrocardiogram throws any light on the stage at which syphilitic myocardial disease becomes detectable. (iii) To compare the results of electrocardiographic and clinical methods of examination in these cases. (iv) To determine the effect of treatment in cardiac syphilis as shown by the electrocardiogram.

Material

The observations were made in the V. D. and Electrocardiographic Departments of the Royal Southern Hospital, and at the Seamen's Dispensary, Liverpool. Cases were chosen irrespective of age and occupation, but entirely from the male sex. A large number were seamen. The history was obtained to exclude the possibility of other diseases, present or past, likely to influence the electrocardiogram. All persons who had previously had any rheumatic manifestations (acute rheumatism, chorea, repeated tonsillitis) were excluded. Other infections, such as diphtheria and scarlet fever, having a doubtful effect on the heart were noted, but the cases were not excluded from the series.

Where possible the date of primary infection was ascertained, the duration and intensity of treatment, the reason for attendance at hospital at the time of examination, and any other relevant features.

A control series of observations on 156 patients was made concurrently. These patients had no cardiovascular symptoms, no history of etiological factors of heart disease, and their hearts on clinical examination were normal in all respects. All electrocardiograms were taken on the same type of instrument: one of the stationary models made by the Cambridge Scientific Instrument Co.

Results

It is to be noted particularly that the cases chosen were patients complaining primarily of *syphilitic* manifestations, not of cardiac symptoms. They thus reported to the venereal clinics and not to the heart clinic. Occasionally it happened that a patient with cardiovascular symptoms reported these at the V. D. clinic, in which case a note has been made of this fact.

All stages of syphilis were investigated as they presented themselves, and the results have been classified according to the grouping of the Ministry of Health.

C. S. = Congenital syphilis.
S 1 − = Primary syphilis with negative Wassermann.
S 1 + = ,, ,, ,, positive ,,
S 2 = Secondary syphilis.
(W. R. +; rashes; lymphadenitis, &c.)
S 3 = Latent syphilis within the first year after infection.
S 4 = Latent and tertiary syphilis any time after the first year from primary infection.

A local classification was adopted at first, but the results were reclassified as above in the hope that they would be more uniform for comparison with those of other workers. The results will be recorded under two headings: (*a*) electrocardiographic variations (the study of which was the principal object of this work); (*b*) incidental observations on clinical changes in the cardiovascular system.

Electrocardiographic Observations.

The total number of syphilitic patients examined, after excluding unsuitable material, was 232, and electrocardiograms were available in 221 cases.

Congenital syphilis (*C. S.*). Seven cases fell into this group. Two showed a tendency to right ventricular preponderance, and two a tendency to left ventricular preponderance. These changes are not considered as outside normal limits.

Primary syphilis. Sero-negative (*S 1* −). In this series, thirty-five cases were examined. Three cases showed definite, and one a tendency to, left ventricular preponderance. One case showed definite, and one a tendency to, right ventricular preponderance. There is nothing to suggest from these observations any variation from the physiological.

Primary syphilis. Sero-positive (*S 1* +). Six cases were examined, but the

electrocardiogram was only available in five. All showed a normal electrocardiogram.

Secondary syphilis (*S 2*). Eighteen cases were examined. Seventeen were electrocardiographed. One showed definite, and one a tendency to, left ventricular preponderance. Case 13 showed a bizarre *Q. R. S.* of low amplitude in Lead I, but this is not considered to be outside normal limits.

Latent syphilis. First year (*S 3*). Forty cases were examined; thirty-four electrocardiographed. Two cases showed definite, and one a tendency to, left ventricular preponderance. One showed a tendency to right ventricular preponderance. Case 27, a man aged 24 years, who had no symptoms or clinical signs of cardiovascular disease, showed negativity of T in Leads II and III (Plate 19, Fig. 1).

Syphilis, latent and tertiary (*S 4*). One hundred and twenty-six cases examined. Electrocardiograms available in all save four. As this series shows a number of gross electrocardiographic defects, these may be conveniently grouped as follows:

Ventricular preponderance.

15 cases showed definite left ventricular preponderance.
8 ,, ,, tendency to left ventricular preponderance.
1 case ,, definite right ,, ,,
1 ,, ,, tendency to right ,, ,,

T-wave defects were seen in two cases, details of which are as follows: Case 116 shows inversion of T in Lead I and a biphasic response in Lead II. The patient was a man aged 49 years who had clinical evidence of aortic regurgitation. The date of primary syphilitic infection was uncertain.

Case 118 shows a T-wave of small amplitude in Lead I and pronounced negativity in Leads II and III. The patient was a negro aged 21 years attending the hospital with gonorrhoea. The Wassermann reaction was positive, but the date of primary infection was uncertain, although in view of the patient's age probably not more than three to four years previously. Treatment was irregular as the patient attended badly. There were no clinical signs of heart disease (Plate 19, Fig. 2).

Three cases showed gross abnormality of the *Q. R. S.* complex (Cases 15, 103, 104). Further, seven cases (11, 23, 42, 81, 84, 92, 98) showed slighter abnormalities of the *Q. R. S.* sometimes in conjunction with other minor deviations from the normal, e.g. left ventricular preponderance. Details of these cases are as follows:

Gross defects. Case 15 shows gross *Q. R. S.* spread, suggesting a partial bundle-branch lesion. The patient was a negro seaman aged 33 years, under treatment for ichthyosis of specific origin. The Wassermann reaction was strongly positive. The history of primary infection was indefinite, but probably occurred seventeen years previously, and there was apparently no treatment. There were no clinical signs of cardiovascular disease (Plate 20, Fig. 3).

Case 103 shows changes suggesting a partial bundle-branch lesion. The patient was aged 48 years, and had an indefinite history as to primary infection. There were no clinical symptoms or signs of cardiovascular disease.

Case 104 also shows electrocardiographic changes suggesting a bundle-branch lesion. The patient, aged 37 years, had syphilis fifteen years previously and was untreated. He applied for treatment for 'fits' in May 1929, and was still under treatment for cerebrospinal syphilis when his cardiovascular system was examined in March 1930. On inquiry he complained of palpitations. The heart was normal in size, the aortic second sound accentuated, and there was a soft apical systolic bruit not conducted to the axilla. The blood-pressure was 141/76, and there was moderate arteriosclerosis.

Minor defects. Case 11 showed slight *Q. R. S.* spread in Leads II and III, with left ventricular preponderance. The patient, aged 39 years, examined in April 1931, was infected twelve years previously, and had a course of treatment lasting three months, but no subsequent treatment until he came to the Royal Southern Hospital in September 1930 with gummata in the left testicle. He has since had continuous treatment. There were no symptoms or physical signs of cardiovascular disease (Plate 20, Fig. 4).

Cases 32, 81, and 84 show minor defects in the *Q. R. S.* complex, but owing to the age of the patients (59, 55, and 57 years) it is not felt that these changes are proved to be due to syphilis.

Case 42 shows a prominent notch on the R in Lead II. The patient, aged 45 years, acquired syphilis twenty years previously. He was attending the V. D. clinic suffering from cerebrospinal syphilis which improved under treatment. There were no other symptoms or physical signs of cardiovascular disease (Plate 21, Fig. 5).

Case 92 shows the *Q. R. S.* notched and of small amplitude, together with left ventricular preponderance. The patient was a fireman, aged 42, who had contracted syphilis six years previously. He had no clinical cardiovascular symptoms or signs.

Case 98 shows notching of R II, and unusually broad summits to P II and III. The patient, aged 48 years, gave an indefinite history of primary infection. There were no clinical symptoms or signs of cardiovascular disease.

It is generally admitted that abnormal rhythms as a result of cardiovascular syphilis are rare, and the following case (106) which came into the present series is of considerable interest, but is considered separately as the patient attended primarily on account of cardiovascular symptoms.

Case 106. The patient, aged 52 years, gave a history of syphilis thirty years previously. He reported November 1929, with a history of anginal attacks since 1926. Clinical examination was difficult owing to emphysema. The first electrocardiogram (November 20, 1929) showed negativity of T II and III and slight *Q. R. S.* spread (Plate 21, Fig. 6 (*a*)). On the same day a record was taken corresponding with an attack of palpitations from which

the patient frequently suffered, and showed paroxysms of ventricular tachycardia (Plate 21, Fig. 6 (*b*)).

After four months' antispecific treatment with bismuth and small doses of kharsulphan, improvement occurred, resulting not only in disappearance of the angina and palpitations, but in abolition of any electrocardiographic evidence of paroxysmal tachycardia. Moreover, the definite negative T II, became a biphasic T (Plate 21, Fig. 6 (*c*)).

The patient continued in this improved condition until 1931, when, whilst walking against a heavy wind one night, he dropped down dead.

Clinical Observations

Groups C S, S 1 −, S 1 +, and S 2 showed no cases in whom cardiovascular disease could be detected by clinical observation.

Group S 3 (latent syphilis first year) included three cases in whom slight cardiac enlargement was present, the apex beat extending between $4\frac{1}{4}''$ and $4\frac{1}{2}''$ from the mid-line in the fifth intercostal space as shown by palpation and percussion. Two of these were young men (24 and 29 respectively), the third, a man of 62, who had considerable arteriosclerosis. None of the three showed any other abnormality, clinical or electrocardiographic.

Group S 4. In this group eight cases were found to have cardiac enlargement of moderate degree without other abnormal signs. Three cases, all in men between the ages of 49 and 50, showed aortic regurgitation, and one diffuse dilatation of the aorta (X-ray).

It should be mentioned that X-ray examinations were not employed as a routine, as the investigation was primarily an electrocardiographic study.

Discussion

In assessing the significance of the electrocardiographic changes a very conservative attitude has been adopted. Only such changes as would be recognized by most authorities as indicative of disease have been included as ' positive ' results. By the examination concurrently of a large group of controls (156) we were able to regard as physiological many minor variations in the electrocardiogram which are regarded by some writers as pathological. Our criteria of abnormality were even stricter than those of Arnett (3). Thus the presence of very small or iso-electric T-waves emphasized by some as evidence of disease was found in sixteen normal cases, whilst slight notching of the R-wave was present in fourteen cases. The *Q. R. S.* in Leads I and II had a low amplitude in as many as twenty-two cases. Such minor variations were therefore counted as physiological. In only two normal persons, however, was a negative T-wave found in Leads II and III, and never in Lead I.

Ten normal cases showed definite ventricular preponderance, and eleven a tendency to this. Of the *syphilitic cases* (221 in all) nineteen showed definite left ventricular preponderance, an incidence only slightly higher than in the controls, and unless accompanied by other material changes in the electrocardiogram little reliance can be placed on ventricular preponderance as an indication of cardiac abnormality.

Serious electrocardiographic defects which leave no reasonable doubt of the diseased state of the myocardium occurred in six cases, all falling into Group S 4, and it is interesting to note that two of the patients were negroes.

Apart from these, electrocardiographic changes which the writers consider suspicious of myocardial damage were present in a further seven cases. One of these (Case 27) occurred in Group S 3, but as an isolated case not too much significance should be attached to it.

The total number of cases of syphilis in whom myocardial damage was detectable by electrocardiographic methods was comparatively small in the present series, but in most of them there was no *clinical* evidence whatsoever of cardiac involvement. Moreover, the number of defects found is considerably greater than Arnett observed in the case of women (4).

It need scarcely be mentioned, on the other hand, that the electrocardiogram is by no means always abnormal in cases even of extensive myocardial disease, and the results of an investigation by this method tend to give the impression of less frequent cardiac involvement than may be the case.

Perhaps the most important point for consideration is the influence of treatment on cardiac syphilis as demonstrated by the electrocardiogram. From the notes of the various cases it will be seen that the majority of the most serious cases are those in whom treatment was absent or irregular. In several instances it was not possible to obtain any information about the treatment. This in itself suggests that it was inadequate.

In none of the cases showing significant electrocardiographic changes was it possible to prove that the patient received adequate treatment during the early stages of syphilis.

Further, we are satisfied that appreciable changes can take place, not only in the clinical condition, but in the electrocardiogram, under the influence of antispecific treatment in patients with syphilitic heart disease.

With regard to the stage of cardiac invasion by syphilis, most authorities have held that cardiac syphilis is essentially a late manifestation of the disease (occurring from fifteen to twenty-five years after the primary stage), and that involvement in the primary, secondary, and early latent or tertiary cases is not proven. From a pathological standpoint Warthin's work suggests that the myocardium is involved with great frequency, as a blood-stream infection, so that the invasion would be *a priori* in the secondary stage.

Our own observations show nothing conclusive to indicate changes in the heart-muscle in the primary or secondary stage of syphilis.

In the latent cases of less than one year's duration, one case shows suspicious electrocardiographic changes (Case 27), but no deduction can be drawn from such an isolated example.

In the later cases, although the majority had a history of syphilis many years previously (twelve to thirty years), two (Cases 118, 92) showed electrocardiographic changes between three and six years after infection, and we believe that an invasion of the heart detectable by electrocardiographic and clinical methods is probably not uncommon within a few years of primary syphilis.

The *clinical examination* of the heart in various stages, though forming a less important feature of the present investigation, revealed several interesting points.

No significant changes were found in the cardiovascular system in congenital syphilis, or in the primary or secondary stages of the disease.

In the latent cases of less than one year's duration some cardiac enlargement occurred in three cases, as already mentioned, and no other cause was found to account for this. Similarly, in Group S 4, eight cases showed cardiac enlargement without other signs and without obvious cause. This observation lends some support to the opinion of certain physicians that 'idiopathic' cardiac hypertrophy is suggestive of cardiovascular syphilis.

The three cases of aortic regurgitation were not remarkable in any way, but it is worthy of note that only one showed an abnormal electrocardiogram (Case 116), emphasizing the necessity of combined clinical and graphic methods of examination if the full incidence of cardiovascular syphilis is to be appreciated.

As a routine, the blood-pressure was taken in most cases, and no difference of moment was found between the syphilitic and control groups.

Symptoms calling attention to cardiovascular disease were found unreliable, and in this paper have been disregarded.

Summary

1. An investigation was made into the electrocardiographic changes occurring in patients with syphilis in all stages. The cases were drawn from venereal clinics and are grouped according to the classification of the Ministry of Health. Incidental clinical observations were made.

2. After excluding unsuitable material, 232 patients with syphilis were examined, and 156 controls. Electrocardiograms were available in all save eleven cases.

3. There was no clinical or electrocardiographic evidence of cardiovascular involvement in congenital syphilis, or in the primary or secondary stages of the acquired disease.

4. Gross electrocardiographic changes were found in six cases, in whom the interval from primary infection varied from three to thirty years.

5. Minor but suspicious electrocardiographic defects were present in a further eight cases. One case occurred within one year from primary infection, the remainder many years later.

6. Aortic regurgitation was found in three patients, in two of whom the electrocardiogram was normal.

7. The total incidence of grave cardiac disease was thus nine cases in 221.

8. Slight cardiac hypertrophy was found by palpation and percussion in eleven instances, three within one year of infection, eight many years after.

These cases showed no other abnormal signs, and may be regarded as giving some support to the opinion that 'idiopathic' cardiac hypertrophy suggests a syphilitic basis.

9. The patients showing gross electrocardiographic defects had received inadequate treatment during the initial stages of the syphilis. Two of them were negroes.

10. Several patients under antispecific treatment showed clinical improvement and a favourable modification of the electrocardiogram.

It is with great pleasure that we acknowledge the kind advice we have received from Dr. John Parkinson and from the late Dr. Carey Coombs. Our thanks are due also to Drs. Fitch and Ross, the heads of the Venereal Departments at the Royal Southern Hospital and the Seamen's Dispensary, Liverpool, who have facilitated our work in their departments. Lastly, we are grateful to Mr. Caldwell for his care and thoroughness in the photographic work of the Electrocardiographic Department.

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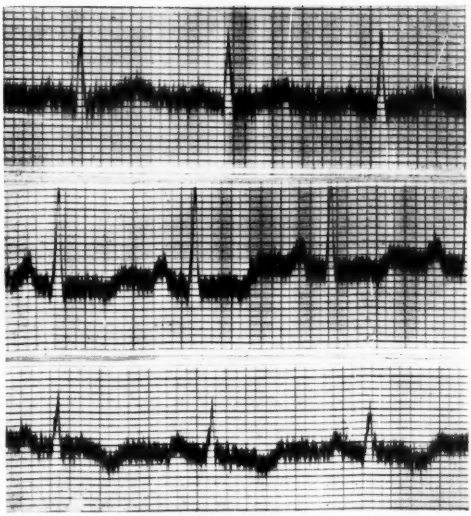

FIG. 1. Shows negative T II and III. Case of latent syphilis within one year of primary infection.

FIG. 2. T I small, T II and III negative. Case of latent syphilis within three or four years of primary infection.

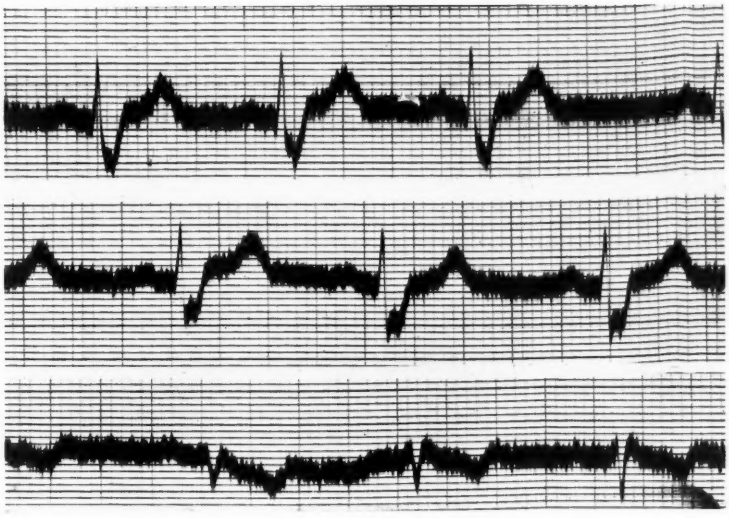

FIG. 3. Shows partial bundle branch block found in patient with specific ichthyosis. Primary infection seventeen years previously. Similar E. C. G. also found in cases 103 and 104, Group S 4.

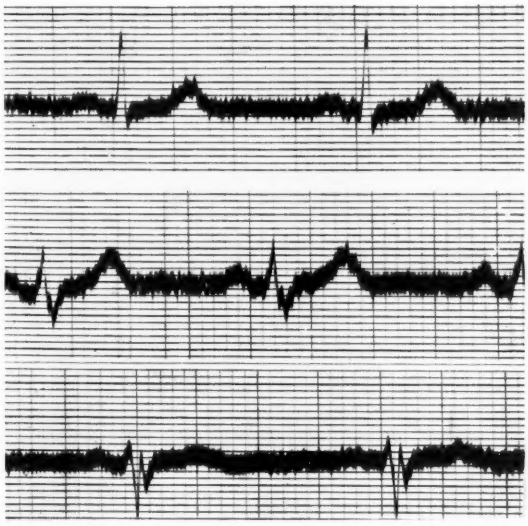

FIG. 4. Shows slight *Q.R.S.* spread Lead II and III with left ventricular preponderance in patient with tertiary syphilis. Primary infection twelve years previously.

FIG. 5. Shows notched R II. Patient contracted syphilis twenty years previously and was under treatment for cerebrospinal syphilis.

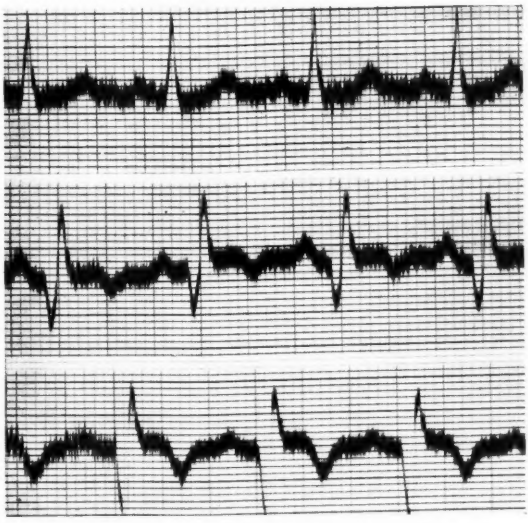

FIG. 6*a*. Shows negative T II and III. Slight *Q.R.S.* spread. Male aged 52 years with angina and palpitations. Syphilis thirty years previously.

FIG. 6*b*. Taken on same day as 6*a*. Showing paroxysms of ventricular tachycardia.

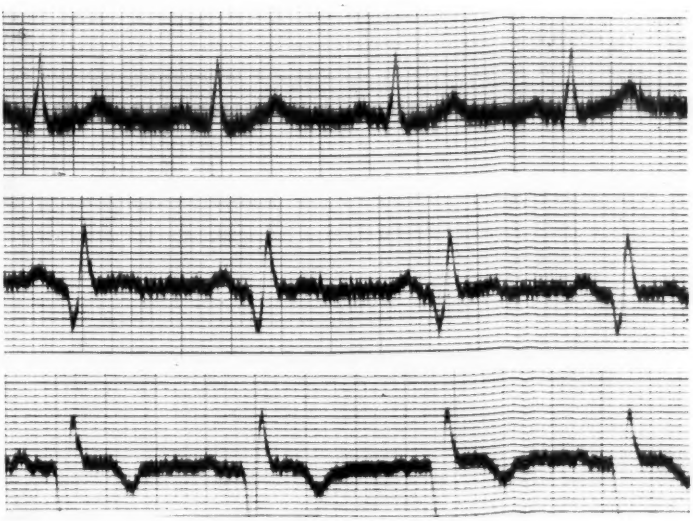

FIG. 6*c*. Taken from same patient as figs. 6 *a* and *b* after four months antispecific treatment. The pronounced negativity of T II, has become a biphasic response.

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RENAL DWARFISM[1]

A REPORT OF 20 CASES WITH SPECIAL REFERENCE TO ITS ASSOCIATION WITH CERTAIN DILATATIONS OF THE URINARY TRACT

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With Plates 23 to 27

In 1883 Lucas (1) observed that 'the phenomena of late rickets and albuminuria are too frequently associated to be matters of chance', but it was not until nearly thirty years later that Fletcher (2) clearly defined the aetiological connexion between chronic kidney disease and bony deformities. Later the work of several observers, notably that of Barber (3), brought about the recognition of renal dwarfism as a definite clinical entity. Barber has defined renal dwarfism as 'a condition of stunted development, associated with bone deformities of the "late rickets" type, due to an insidious chronic interstitial nephritis of obscure aetiology'. Although the designations renal dwarfism, renal infantilism, and renal rickets are used synonymously for this group of cases, one of them may often be more accurately descriptive of any given case, depending on whether dwarfism, infantilism, or rickets is the presenting clinical feature. At the present time about eighty examples of this condition are recorded.

In the course of a systematic investigation of nephritis at the London Hospital we have observed a number of cases of renal dwarfism and have noticed that in addition to the familiar small, fibrotic, contracted kidneys found in these cases, there occurred in most instances a marked dilatation and hypertrophy of the bladder accompanied usually by varying degrees of hydronephrosis and dilatation of the ureters, this dilatation occurring in the absence of any obvious obstruction. The object of this paper is therefore twofold; first, to report twenty cases of renal dwarfism, all but two of which (Cases 17 and 18) are hitherto unrecorded, and, secondly, to call attention to the association of this syndrome with an unexplained dilatation of the urinary tract.

Analysis of Case Reports

Twelve of the cases reported in this paper were seen by us during life; 8 of these have since died, and of these 6 have come to autopsy. A search

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of the records of post-mortem examinations made in the period 1913–32 inclusive (Bernhard Baron Institute of Pathology) revealed a further 8 cases, making 20 cases in all. Analysis of these 20 cases revealed the following facts:

Age of onset. The average age at which the patient first came under observation was about 12½ years. Lathrop (6) in a review of 14 cases finds this same average. Maddox (7), however, in a review of 84 cases from the literature, places it at 7 years. The average age of the onset of symptoms in our series was 9½ years, but many had symptoms in early infancy or were noted to be small from birth; the average age at which genu valgum developed was 12½ years.

Of our 20 cases, 12 were males and 8 females. There is no appreciable difference in the sex incidence in the cases reported in the literature. A family history of renal disease was present in 4 of our cases. Two of Barber's (3) patients were brother and sister.

Symptoms. Thirst, polyuria, nocturnal enuresis, failure to grow, and the appearance of bony deformities were among the more common complaints. Gross haematuria occurred in 3 cases; renal pain in 2; and incontinence of urine by day and night in 1. Later, uraemic symptoms such as headache, vomiting, a tendency to haemorrhages, coma, and occasionally fits, occurred, 15 of our cases terminating in this way. Shortness of breath, palpitation, and disturbance of vision were rare; they occurred only in the two cases which showed marked arterial hypertension. Mental dullness and backwardness were present in 3 cases, 1 was very bright and intelligent, and 9 were of average mentality. A history of oedema or of illness resembling acute nephritis was noticeably absent in all cases. Beyond occasional reports of slight puffiness of the eyes, no history of the previous occurrence of oedema was obtained.

Signs. 'Rickets'. Bone changes were present in 15 cases; genu valgum in 9, and genu varum in 3; other 'rachitic' changes found were 'bossing' of the frontal bones, enlargement of costochondral junctions, Harrison's sulcus, enlarged epiphyses at the wrists, knees, and ankles, and bending of the long bones.

Dwarfing. This was present in 14 cases. In one case it was marked, in the absence of any evidence of rickets. The dwarfing is rarely extreme, and is usually manifested by a mere retardation of growth.

Infantilism. This was recorded in 7 cases. It presented in the following ways: juvenile appearance, high-pitched voice, lack of pubic and axillary hair, absence or retarded development of secondary sex characters, scanty catamenia, infantile uterus, unscarred ovaries, and hypoplastic testicles.

The relative frequency of occurrence of these three manifestations, rickets, dwarfism, and infantilism, and their association with one another, and the relationship of changes in the serum calcium and plasma phosphorus to the occurrence of 'rickets', are shown in Table I.

Pigmentation. Discoloration of the skin was a prominent feature, it being

specifically noted as yellow, greyish yellow, brown, sallow, or pale in 14 cases. Dryness and coarseness of the skin were not uncommon. In one case (Case 20) no discoloration or dryness of the skin was present.

TABLE I

The Relative Association of Rickets, Dwarfism, and Infantilism

Case no.	Manifestations of rickets, dwarfism, and infantilism.	There were no observations on serum calcium and plasma phosphorus in these cases	Case no.	Manifestations of rickets, dwarfism, and infantilism.	Serum calc. in mg. %; max. and min. values.	Plasma phosph. in mg. %; max. and min. values.
1	D.R.		10	D.I.	3·8 latent tetany	26·7
2	D.R.I.		11	D.R.I.	7·4-5·0	3·5–7·0
3	D.I.		13	D.	8·7	—
4	D.		14	D.R.	6·3–5·4	5·3–9·0
5	R.		15	R.	8·0	4·0
6	D.R.		16	D.R.I.	9·4–8·6	4·0–5·8
7	R.		17	D.R.	8·5	4·3
8	D.		18	D.R.	9·8	3·5
9	R.I.		19	R.	6·7 latent tetany	5·1
12	R.I.		20	D.R.	10·5–7·6	4·0–5·8

R = Rickets. D = Dwarfism. I = Infantilism.

Oedema. Slight puffiness of the eyes was noted in 3 cases; in one of these, a child with a severe infection of the kidney and much pus in the urine, there was also slight oedema of the back and legs.

Anaemia. Of 11 cases in which the blood was examined, 10 showed a moderate to severe secondary anaemia; one was peculiar in the absence of anaemia (Case 17).

Arteries. Thickening of the brachial and radial arteries was noted clinically in 8 out of 12 cases; there was no record in the remaining cases.

Heart. Cardiac enlargement was noted clinically in 3 cases; it was marked in the two cases with marked hypertension and slight in another (Case 9). Some degree of hypertrophy of the left ventricle was found at autopsy in 11 out of the 14 cases examined.

Blood-pressure. Marked hypertension was present in the two cases which showed marked clinical enlargement of the heart: one a girl with 16 years' history of 'pyelitis' (Case 7), and the other a worker in lead (Case 12). In 3 others the blood-pressure was above normal, 150/70 (Case 13), 145/110 (Case 14), and 130/90 (Case 9); in 2 of these the pressure fell to normal in a few days following rest in bed. In the 9 remaining cases in which the pressure was recorded there was no hypertension.

Retinitis. The fundi were examined in 12 patients, only 2 showed retinitis. These were the two with marked arterial hypertension.

Urine. Low specific gravity was a constant finding. Albuminuria was found consistently in all cases with two exceptions, one a case in which no record of urinary examination could be traced, and another reported 'clear' by the clinical clerk on one examination only. Cases in which albuminuria was

not consistently present have been recorded in the literature; we have never observed this. Gross haematuria occurred in 3 cases; pus was present in 6 cases; organisms were cultured in 6 cases, *Staphylococcus albus* in 3, paracolon bacillus in 2, and the *Bacillus coli* in 1. Occasional red cells, leucocytes and epithelial cells were common findings in the urinary deposits.

Renal function. The blood urea was recorded in 15 cases; it was always raised, varying from 73 to 663 mg. per 100 c.c. The renal-function tests in all cases showed impaired excretion of phenolsulphonephthalein and impaired urea concentration.

Calcium and phosphorus. The serum calcium and plasma phosphorus were estimated in ten cases. The results were abnormal in all but one. The maximal and minimal calcium and phosphorus values obtained and their relation to the occurrence of bone changes are shown in Table I. It will be seen that 'rickets' occurred in 1 case though the calcium was normal (Case 18), a renal origin of the 'rickets' in this case is doubtful. 'Rickets' was occasionally absent on the other hand when the calcium was definitely diminished (Cases 10 and 13). Latent tetany was observed in 2 cases, in both a low calcium was present.

Urinary system. The kidneys, ureters, and bladder were examined at autopsy in 14 cases and radiologically during life in 4 cases; one of the latter is included among the autopsies, so that in all we have to consider these observations on a series of 17 cases.

Evidence of moderate to severe degrees of hydronephrosis, dilatation of ureters, or hypertrophy and dilatation of the bladder was found in 14 cases; in 11 of these the pelves, ureters, and bladder were all involved; in 2 the bladder only was affected; and in one case in which the bladder alone was examined a cystogram showed gross dilatation (Case 20). In addition there was a double pelvis and ureter on the left side in one case (Case 13); and in another (Case 19) an abnormal position of dilated ureteric orifices was present. There was macroscopic post-mortem evidence of infection in 5 cases. In no case was any obvious obstruction to the outflow of urine discovered.

The remaining 3 cases showed the following:

Case 3. There was no record of the appearance of the pelves, ureters, or bladder at autopsy, so that the absence of gross pathological change may be presumed.

Case 7. A girl with sixteen years' history of 'pyelitis' who showed on clinical examination hypertension and retinitis. At necropsy the pelves, ureters, and bladder were normal.

Case 17. A cystogram showed 'a somewhat over-distended bladder', but there was no abnormality of shape nor ureteric reflux. The bladder was considered to be within the limits of normal. Pyelography was not done in this case, so that no evidence as to the pelves and ureters is available.

The kidneys in all 14 cases examined at autopsy were small and fibrotic with complete loss of normal pattern. They showed large regeneration nodules. No demonstrable difference was apparent to the naked eye in

the one instance in which dilatation of the tract was absent. In the surviving cases renal insufficiency was present in every instance.

Discussion

Renal dwarfism would seem to result from prolonged intoxication due to deficient renal function occurring during the age of growth. The changes in the bones are thought to be associated with phosphorus retention, which in turn leads to a low blood calcium ; more recently, American workers (8) have suggested that there is also a shift of the excretion of endogenous phosphorus to the intestines, resulting in deficient calcium absorption and true calcium starvation. It would therefore appear probable that any chronic kidney lesion leading to prolonged renal insufficiency in a growing child may give rise to these metabolic disturbances. In the cases previously reported, chronic nephritis with contracted kidney is the lesion usually described (9) ; in occasional instances such conditions as renal calculi (10), phimosis (11), congenital malformation of the urethra (12) are reported. Several observers have mentioned the finding of gross dilatation of the urinary tract in individual cases (13).

In this series of 20 cases the striking feature is the occurrence of an unexplained dilatation of the urinary tract in most of the cases. The urinary tract was examined in 17 of the 20 cases ; in 14 dilatation of part or the whole of the tract was present. As the bladder was involved in all these cases, the urinary retention, to which the dilatation is presumably due, must result from obstruction below this level. In no case was any obvious obstruction found ; nor was any abnormality of the nervous system detected. This suggests that the underlying lesion is a functional failure of the vesico-urethral sphincter, either the occurrence of spasm or, as is more probable from what is found elsewhere, a failure of relaxation. A neuromuscular defect has been suggested by several observers (14) as the cause of so-called ' congenital ' hydronephrosis. Hurst (15) has reported a case showing dilatation of the pelvis and ureter of one kidney ; he called the condition achalasia of the uretero-vesical sphincter, and compared it to the similar dilatations occurring in the oesophagus and colon. A neuromuscular defect might be either congenital or acquired ; in two examples not included in this series we have found the condition *post mortem* in infants aged 3 weeks and 6 months respectively. This early incidence of dilatation suggests a congenital origin at least in some cases.

The origin of the condition must be regarded, however, as still uncertain. The solution of the problem is complicated by the fact that in all the cases we have examined histologically the kidneys show, in addition to the signs of hydronephrosis with resulting compression atrophy, the appearances which we associate with a nephritis. We do not propose to discuss the histological findings in this paper, the destruction of the kidneys in most instances is so

advanced that the interpretation of these findings obviously presents great difficulties. We have therefore considered it advisable to state only the facts that appear from clinical and gross morbid anatomical examination. Poynton and Sheldon (16) have investigated the causes of dilatation of the bladder and urethra in childhood and have reported several cases in which no cause of obstruction was found. They suggest that mechanical causes of obstruction, such as a posterior urethral valve, are easily missed, and plead for the removal of the urethra in continuity with the bladder in post-mortem examination of all cases showing urinary tract dilatation. This is a routine procedure at the London Hospital and was carried out in every instance in this series. In no case was any evidence of a mechanical cause of obstruction found. It should be realized that these dilatations were noted in the course of routine post-mortem examinations. Except in a few recent instances, their occurrence was not expected ; their finding, therefore, was not the result of special search. This makes the relative constancy of their occurrence even more striking.

The frequent occurrence of renal dwarfism, in association with these dilatations of the urinary tract, is due probably to the early age at which the disorder occurs, the slow progress of the disease, and the remarkably long period over which severe renal insufficiency may persist in this condition. One of our patients, now aged 14 and still attending school, when examined in 1927 had a blood urea of 90 mg. per 100 c.c. A year later, and again two years later, a similar figure was recorded. In 1931 the blood urea was 130 mg. per 100 c.c., and on December 30, 1932, 103 mg. (Case 20). Barber (17) has called attention to the very long duration of renal insufficiency in these cases, and Cockayne and Wood (18) have reported a case with a blood urea constantly over 100 mg. during a period of three and a half years. We have noted the same phenomenon in a patient with congenital cystic disease of the kidneys, who has remained regularly at her work during the past two and a half years though the blood urea has been constantly more than 100 mg. per cent. This tolerance to the results of renal insufficiency is in striking contrast to that seen in chronic nephritis in which death usually occurs within a few months of the onset of pronounced renal insufficiency. The difference is probably associated with the presence of arterial hypertension in the latter condition.

In our cases of renal dwarfism arterial hypertension was noticeably absent ; the associated manifestations, cardiac enlargement, breathlessness, disturbance of vision, and albuminuric retinitis also rarely occurred. This is in agreement with most of the reported cases (3). In only two of our patients was marked hypertension present. Both these patients showed also cardiac enlargement, breathlessness, and retinitis (Cases 7 and 12). It is noteworthy that one of these patients (Case 7) is the one patient in the series in whom dilatation of the urinary tract is definitely recorded as absent ; and that the other was a worker in lead, and that lead was found in his urine.

In a subsequent paper, in which we shall present the analysis of the

records of all patients under 30 years of age who showed contracted kidneys at necropsy in the period 1913–32 inclusive, we propose to elaborate the relation between hypertension and these different kidney lesions. In that paper we shall produce evidence suggesting that the widely held opinion, especially sponsored by Rose Bradford (19), that hypertension is often absent in children with contracted kidneys, is probably applicable only to this type of lesion in which dilatation of the urinary tract occurs; and that the contracted kidney of true insidious nephritis is accompanied, in children as in adults, by arterial hypertension.

Summary

1. Twenty cases of renal dwarfism, two only of which have been previously recorded, are reported.

2. In seventeen of these cases observations on the urinary tract were available; fourteen showed varying degrees of dilatation, which in some cases were extreme.

3. The urinary retention appeared to occur at the level of the urethro-vesical sphincter. No obvious cause of obstruction or lesion of the nervous system was found. A disorder of the neuromuscular mechanism controlling the urethro-vesical sphincter is suggested.

4. The frequent association of renal dwarfism with this type of lesion is explained by the occurrence of long persisting renal insufficiency in this condition.

5. Arterial hypertension is uncommon in patients with renal dwarfism. When it does occur it is probably in the somewhat rare instances in which this condition is associated with a true contracted kidney due to chronic insidious nephritis.

Case Reports.

Case 1. (J. B.)* A boy, aged 13 years, was admitted under the care of the late Sir Frederick Eve. He complained that his legs had been getting bowed outwards for the past twelve months. Previously he had always been well. His parents were healthy and there were seven other children alive and well.

On examination he was small for his age, looking about the size of a boy aged 8 years; his height was 3 ft. 11 in. There was marked bilateral genu valgum, causing 4½ in. separation of the internal malleoli when the knees were together. *Urine.* Pale; S. G. 1010; albumin, a trace.

He was considered unfit for operation. During the second week after admission he began to vomit, showed a tendency to anuria, and died in uraemia.

Post mortem: Urinary system. Very small pale kidneys (2¼ oz.), showing wide dilatation of pelves and areas of extremely narrow cortex and medulla alternating with nodules of hypertrophied cortex. Dilatation of ureters

(0·6 cm. diam.). Chronic cystitis with hypertrophy of bladder. *Heart.* Concentric hypertrophy of left ventricle (R. V. 0·3 cm., L.V. 1·4 cm.) (weight 7 oz.). *Skeleton.* Genu valgum (28°). Cranial cavity small. *External appearance.* Face large, flat, and coarse; looks about 8 yrs.; height 3 ft. 11 in.; weight 44 lb. P.M. No. 196/13. *Reg. No. 10930/13.

Case 2. (A. R.)* A girl, aged 17 years, was admitted under the care of the late Sir Frederick Eve. She complained of bending of the legs.

On examination she was a badly developed girl, 4 ft. 9 in. in height. There was well marked genu valgum. *Urine.* Pale; S. G. 1010; albumin, a slight cloud.

Osteotomy was performed on the right side. She developed uraemia and died ten days after operation.

Post mortem: Urinary system. Extreme fibrosis with scarring of kidneys (3½ oz.); hydronephrosis; large hyperplastic nodules of kidney substance at upper pole of both kidneys. Slight dilatation of ureters. Hypertrophy of urinary bladder with chronic inflammation and pigmentation of mucosa; small papilloma of urinary bladder above orifice of right ureter. *Heart.* No hypertrophy (weight 8 oz.). *Skeleton.* Osteotomy for genu valgum at lower end of right femur; upper end of bone overlapping lower; no callus at cut end of bone. *Genital system.* Infantile uterus with unscarred ovaries. *Nervous system.* No macroscopic abnormality in lumbar cord or cauda equina. *External appearance.* Thin, badly developed girl; height 4 ft. 9 in.; weight 64 lb. P.M. No. 274/14. *Reg. No. 20134/4.

Case 3. (J. B.)* A boy, aged 12 years, was admitted under the care of Sir Henry Head. The day before admission he had had a fit, followed by two more fits on the day he came into hospital.

On examination he was a poorly developed boy, 3 ft. 7 in. in height; he looked about 6 years old. The tongue was foul and the gums were bleeding. There was no abnormality in the heart. Both testicles were undescended. *Urine.* No record.

Soon after admission he became unconscious and died on the third day.

Post mortem: Urinary system. Minute pale kidneys (1¼ oz.) with slightly adherent capsule and nodular subcapsular surface; on cut surface a granular cortex with almost complete destruction of cortical and medullary pattern; minute lipoid flecks in cortex. *Heart.* Slight hypertrophy of left ventricle (1 to 1·2 cm.) (weight 5 oz.). *External appearance.* A spare badly developed child; height 3 ft. 7 in.; weight 38 lb. 6 oz. P.M. No. 256/14. *Reg. No. 30794/14.

Case 4. (N. W.)* A girl, aged 14 years, was admitted under the care of Lord Dawson. The night before admission she had had a 'blue fit' and difficulty in breathing.

On examination she was a poorly developed girl, 4 ft. in height. She was found to have laryngeal diphtheria, from which she died on the following day. *Urine* (only reported by clerk once). S. G. 1018; albumin, nil.

Post mortem: Urinary system. Very small fibrotic kidneys (2½ oz.) with nodules of hypertrophy; double hydronephrosis. Dilatation and slight hypertrophy of both ureters. Great hypertrophy and dilatation of urinary bladder. No obstruction in urethra. *Heart.* No hypertrophy (4¼ oz). *External appearance.* Rather aged looking face; thin, poorly developed girl; height 4 ft.; weight 45 lb. 6 oz. P.M. No. 132/15. *Reg. No. 40573/15.

Case 5. (C. D.)* A boy, aged 8 years, suffering from genu valgum, was admitted under the care of Mr. Milne.

No record of physical examination is available. *Urine.* Pale; S. G. 1008; albumin, a trace; naked eye deposit of pus.

Operation, bilateral osteotomy for genu valgum, was performed, and he died in uraemia five days later.

Post mortem: Urinary system. Great hydronephrosis with atrophy and fibrosis of greater part of renal substance; anaemia, oedema, and fatty degeneration of nodular hypertrophy of remainder (kidneys 2 oz.). Great dilatation and hypertrophy of ureters (3·5 cm. circumf.). Great hypertrophy and dilatation of urinary bladder. No macroscopic evidence of inflammation of bladder, ureters, or renal pelves. No obstruction in urethra or at meatus. *Heart.* No hypertrophy (3¼ oz.). *Skeleton.* Soft deep (0·5 cm.) bulging crenated zone of proliferating cartilage between lower epiphysis and diaphysis of right femur, with no visible zone of provisional chondral calcification; zone (0·8 cm. deep) of denser, partly osteoid, bone in metaphysis. Soft deep (0·35 cm.) bulging crenated zone of proliferating cartilage in neck of right femur; zone of proliferating cartilage (0·1 cm. at deepest) beneath great trochanter; provisional chondral calcification visible in upper metaphysis of right femur. Zone (0·5 cm. deep) of denser slightly osteoid bone in metaphysis of ribs; zone of provisional calcification crossing proliferating cartilage of ribs. No appreciable softening of calvaria (0·2 to 0·25 cm. thick). Shaft of femur straight. No deformity in other bones. *Nervous system.* No abnormality in brain or spinal cord. *External appearance.* Thin, pallid boy; height 3 ft. 1 in.; weight 30 lb. P.M. No. 284/16. *Reg. No. 12164/16.

Case 6. (A. B.)* A boy, aged 8 years, was admitted under the care of Mr. Milne. He had been born at full term, had been bottle fed, and had always been small for his age. He had always complained of thirst. Nine months before admission he had begun to limp and to be unable to use his arms properly.

On examination he was a small, thin, pallid child, 3 ft. 2 in. in height and 2 st. 12½ oz. in weight. His intelligence was normal. There was enlargement of the wrists with ulnar deviation of the hands; the upper limbs could not be held above the horizontal position; the knees could not be straightened beyond 165°. There was slight 'beading' of ribs. The heart was not enlarged; the systolic blood-pressure was 110. The fundi were normal. *Urine.* Pale; S. G. 1002; albumin, 1/8 volume; deposit, red cells. *Blood urea.* 0·246 per cent.; P. S. P. and urea concentration: first hour, trace; second hour, trace and 0·66 per cent. in 52 c.c.; third hour, trace and 1·02 per cent. in 53 c.c. *X-ray of bones.* Gross failure of calcification of epiphyseal lines in wrists, shoulders, knees, and ankles. Backward separation of lower epiphyses of femur and fracture separation of upper epiphyses of humeri. Ulnar displacement of both radial epiphyses. Upward rotary displacement of lower tibial epiphyses.

This patient died in uraemia some months later at an infirmary.

Post mortem: Urinary system. Extremely small kidneys (left 4·2 × 2·6 × 1·2 cm.; right 3·9 × 2·6 × 1·8 cm.) (weight 20·5 grm.) with transparent capsule; very narrow completely granular pale grey, slightly injected cortex with opaque white areas and no visible cortical pattern; indistinct demarcation, faint straight pattern and opaque white streaks in grey gelatinous medulla (C/M = 1/4·5). Moderate dilatation and hypertrophy of bladder (7 cm. circumf.

and 0·35 cm. thick). No abnormality in urethra. *Heart.* Considerable hypertrophy, especially left ventricle (3¾ oz.). *Skeleton.* Marked ulnar deviation of wrists; prominent heads of humeri; knees held partly flexed. Heads of femora crushed downwards and outwards into shafts at expense of necks. Tibial articular surface for astragalus directed outwards. Left humerus larger than right. Heads of humeri crushed downwards and outwards at expense of necks. Lower end of each radius directed inwards beneath lower end of ulna. Thickening of costochondral junction of ribs, sometimes more prominent on inner surface. On section: lower end of humerus, upper end of radius, upper end of ulna, upper end of fibula apparently normal; deep zone of proliferated cartilage, bounded laterally by resting cartilage, in lower end of radius and ulna, in both ends of tibia and lower end of femur; similar zone of proliferated cartilage and irregularly disposed proliferated cartilage in metaphysis, in head of humerus, head of femur, lower end of fibula, and in ribs. *Genital system.* Hypoplasia of testicles (body 1·7 × 0·8 × 0·7 cm.). *External appearance.* Undersized moderately nourished boy; height 3 ft. 2½ in.; weight 2 st. 8 oz. P.M. No. 238/26. *Reg. No. 12588/25.

Case 7. (M. C.)* A girl, aged 18 years, was admitted under the care of Lord Dawson. There was a history of rickets with 'bending of the leg bones' at the age of 9 months. Polyuria and enuresis had been constantly present since the age of 2; at this time (1910) she was for five months an in-patient in King's College Hospital with pyelitis, with pus and *B. coli* in the urine. She was again an in-patient in the same hospital in 1912 when a large amount of pus was found in the urine. At this time a lump was felt in the abdomen below and to the left of the umbilicus; a tentative diagnosis of tuberculous pyelitis was made, but no tubercle bacilli were found in the urine. No further history of this patient is known until six months before admission to the London Hospital in 1926 when she began to complain of gradually increasing dimness of vision and headache. One week before admission she had epistaxis, morning vomiting, shortness of breath, and palpitation.

On examination she was a well developed but small girl with a dry yellowish skin. The heart was enlarged, the apex being ½ in. external to the nipple line. Blood-pressure 210/145. The fundi showed 'albuminuric retinitis'. *Urine.* Albumin, ½ volume; deposit, red cells and leucocytes. *Blood urea.* 0·408 per cent.; P. S. P., no trace in three hours; urea concentration 0·99 per cent. in second hour, and 0·96 per cent. in third hour.

This patient died in uraemia eight days after admission.

Post mortem: Urinary system. Very great reduction in size of kidneys (right 1½ oz.; left 1 oz.) with considerable adherence of capsule to roughly nodular subcapsular surface, the latter surface showing a few cysts (up to 1·0 cm. diam.) and pale yellowish-grey translucent regeneration nodules (up to 0·7 cm. diam.); very great reduction in width of completely patternless red somewhat congested cut surface of cortex (0·7 cm. wide); further focal reduction of cortex (0·3 cm. wide) associated with focal dilatation of calyces most noticeable at poles of kidneys; a few submucous haemorrhages in otherwise normal renal pelves; very sparse lipoid flecking in pale yellowish-grey regeneration nodules (up to 1·0 cm. diam.) in the columns of Bertini. Numerous opaque yellow streaks in medullary pyramids. Considerable prominence of vessels in neighbourhood of completely blurred line of demarcation. No abnormality in bladder, except slight injection of mucosa. *Heart.* Considerable hypertrophy of heart, most marked in left ventricle

(weight 11½ oz.). *Skeleton.* No visible deformity. Collection (4·0 × 1·3 cm.) of rounded nodules (up to 0·6 cm. diam.) of firm translucent bluish-grey cartilage occupying upper end of shaft of right femur, the upper pole of the collection lying 6·2 cm. below the great trochanter. Soft red marrow occupying shaft about the nodules of cartilage. Streaks of pinkish red mixed with yellow fatty marrow throughout middle 10·0 cm. of 30·5 cm. femur. No visible abnormality in left femur or in right or left tibia. Fatty marrow throughout shafts of both tibiae. Slight discoloration and transverse ridging of teeth. *Nervous system.* Cyst (0·7 cm. diam.) containing firm honey-like content on superficial aspect of pars intermedia of pituitary (0·6 grm.). *External appearance.* Very sallow, moderately wasted, well built woman; height 5 ft. 2½ in.; weight 88 lb. P.M. No. 502/26. *Reg. No. 40958/26.

Case 8. (M. A.)* A girl, aged 8 years, was admitted under the care of Mr. Neligan. She had never grown properly and had always been ailing since she was an infant of 2 years. Recently she had complained of attacks of pain in the loins.

On examination she was a pale, stunted child, 3 ft. 8½ in. in height, and looked about 4 or 5 years old. The tongue was furred and the skin dry. *Urine.* Acid; S. G. 1005–10; albumin, a heavy cloud; deposit, few red cells, and pus cells; culture *Staphylococcus albus. Blood urea.* 0·22 per cent. Soon after admission she got rapidly worse, with vomiting and fits; she died in uraemia two weeks later.

Post mortem: Urinary system. Very small kidneys (right 5·2 × 2·7 × 1·7 cm.; left 6 × 3 × 2 cm.) with moderately dilated pelves (each 3·5 cm. circumf.); dilatation of calyces, and great destruction of renal tissue, especially of right kidney. Abundant renal tissue in upper poles and in middle part of left kidney, showing creamy white patternless cortex, blurred demarcation, pink medulla, and very profuse lipoid flecking. Dilatation (up to 2·5 cm. circumf.) with thickening of grey faintly granular mucosa of both ureters. Hypertrophy and dilatation of bladder (7 cm. diam., 0·5 cm. thick) with a uniformly crimson slightly granular mucosa. Injection of urethra; no obstruction of urethra. *Heart.* Considerable hypertrophy of left ventricle (L. V. 1·4 cm.; R. V. 0·3 cm.; weight 5¾ oz.). *Nervous system.* No abnormality in spinal cord or cauda equina. *Skeleton.* No asymmetry or other abnormality. *External appearance.*[2] Moderately nourished, well developed girl with smooth, soft skin; height 3 ft. 8½ in.; weight 36 lb. P.M. No. 309/27. *Reg. No. 22436/27.

Case 9. (E. H.)* A girl, aged 16 years, was admitted under the care of Professor Ellis. She had been well until three months before admission when she had had an attack of influenza. At this time she had been in bed for a period of two weeks with sore throat, headache, and fever; there had been no disturbance of micturition. Two months before admission she had begun to complain of slight puffiness of the face, headaches, and vomiting. There was no history of any urinary disturbance at this or any previous time. She had begun to menstruate at the age of 14 years and her periods had been regular until nine months before admission, when amenorrhoea developed. She had always been mentally dull. Six years before this admission she had been admitted to hospital following a street accident; a torn splenic artery was found at laparotomy and splenectomy was performed; at this time the examination of the urine revealed the presence of albumin.

[2] Compare with physical examination.

On examination she was a poorly developed girl, 5 ft. 1 in. in height and 6 st. 7 lb. in weight. There was bronzing of the skin of the whole body. The axillary and pubic hair was scanty. The breasts were small. The uterus felt small on rectal examination. There was genu valgum. The arteries were not thickened. The heart was slightly enlarged. The blood-pressure was 130/90. There was a congenital anomaly at the margin of the right disc, otherwise the fundi were normal. *Urine.* Pale; S.G. 1008; albumin, a cloud; deposit, occasional leucocytes and epithelial cells; culture, *Staphylococcus albus. Blood urea.* 0·28 per cent.; P.S.P. nil in three hours; urea concentration 0·63 per cent. in 158 c.c. at third hour. *Blood count.* Red cells 1,900,000; haemoglobin 38 per cent.; colour index 1·0; leucocytes 9,000; polymorphs 84·0 per cent. *Blood Wassermann test.* Negative.

This patient died in uraemia twelve days after admission.

Post mortem: Urinary system. Kidneys (right 1 oz., left 1¾ oz.) greatly reduced in size; capsule strips easily, leaving an irregularly nodular pink or greyish-white subcapsular surface; great reduction of both cortex and medulla; cut surface of cortex smooth, pale yellowish-white, patternless, and flecked with areas of injection and petechiae, especially in the right kidney; great blurring of demarcation and distortion of relation between pyramids and their cortex; great blurring of medullary pattern, least in the tips of pyramids; numerous slightly opaque yellow chronic abscesses in the form of nodules (from 0·2 to 0·7 cm. diam.), occasionally in the form of streaks and wedges, especially in cortex, but also in medulla and in the peripelvic fat between the pyramids, the abscesses bulging but not exuding pus on pressure. Injection of slightly dilated renal pelves and slight flattening of a few pyramids. Slight dilatation (0·7 cm. circum.) and injection of ureters. Numerous patches of injection in mucosa of hypertrophied bladder (1·0 cm. thick). No obstruction of urethra. *Heart.* Considerable hypertrophy (11 oz.). Dilatation of right ventricle, slight of left ventricle. *Skeleton.* Pink marrow containing a large proportion of fat in upper half of shaft of tibia and in shaft of fibula. Cartilaginous epiphyseal junction (0·25 cm. deep) at lower end of femur, finely crenated on its diaphyseal surface and showing an opaque white zone of calcification (0·05 cm. deep) in part of this surface; cartilaginous epiphyseal junction (0·1 cm. deep) at upper end of humerus with a nodule of cartilage (1·0 cm. deep) projecting from it near its middle into the metaphysis. Traces of apparently normal cartilaginous epiphyseal junction present at upper end of tibia and also at lower end of fibula. *External appearance.* Slight diffuse brown pigmentation of skin; operation scar to right of umbilicus; height 5 ft. 1 in.; weight 84 lb. 10 oz. P.M. No. 230/29. *Reg. No. 40773/29.

Case 10. (K. P.)* A boy, aged 11 years, was admitted under the care of Dr. Theodore Thompson. He had always been small and debilitated; he bruised easily. His mother had died of consumption; his father and six other children were alive and well. For the past three months he had complained of frequent headaches, drowsiness, and listlessness; for ten days his tongue had felt swollen and painful and he had had abdominal pain and epistaxis. He had vomited large quantities of a coffee-coloured fluid the day before admission.

On examination he was a small boy for his age, height 46 in., with a pale, slightly yellow-tinted skin and marked anaemia of mucous membranes; his tongue was swollen and the gums were bleeding. There was no axillary or pubic hair, and the external genitalia were small. There were no signs of

rickets. The brachial and radial arteries were considerably thickened, but there was no obvious cardiac enlargement; the blood-pressure was 120/80. No abnormality was seen in the fundi. Chvostek's sign was positive; Trousseau's sign was negative. There were several bruises on the limbs. *Urine.* Pale; S. G. 1012; albumin, 1/7 volume. *Blood count.* Red cells 1,800,000; haemoglobin 30 per cent.; colour index 0·83; white cells 15,240; polymorphs 89·5 per cent.; eosinophils 0·5 per cent.; small lymphocytes 4·5 per cent.; large lymphocytes 3·5 per cent.; large hyalines 0·5 per cent.; trans. neutrophils 0·5 per cent.; neutrophil myelocytes 1 per cent. Bleeding time 6½ minutes. Van den Bergh, negative direct and indirect. Fragility normal. Reticulocytes 0·5 per cent. *Blood urea.* 0·663 per cent. *Serum calcium* 3·8 mg. per cent.; serum phosphorus 26·75 mg. per cent.; serum phosphatase 0·279. (These specimens were taken shortly before death.)

He gradually became comatose and died four days after admission.

Post mortem: Urinary system. Small kidneys (left 7·3 × 3·5 × 2·5 cm.; right 6·0 × 4·0 × 2·2 cm.) (weight 2¼ oz.) with irregular subcapsular surface showing a pink sunken reticulum between pale yellowish-white flat nodules (0·25 cm. diam.), and numerous petechiae; on the cut surfaces a very narrow coarsely-granular pale yellowish-white cortex (0·2 cm. deep), indistinct demarcation, and pale pink medulla (0·5 cm. deep) with blurred pattern. A few petechiae in trigone of dilated (14·0 cm. circumf.) bladder; hypertrophy and slight trabeculation of bladder (muscle 0·25 cm. thick); no obstruction to outflow of urine. *Heart.* Moderate hypertrophy of left ventricle; weight 6 oz. *Skeleton.* Normal osteochondral junctions in ribs, right femur, fibula, humerus, radius, and ulna; vertebral column normal; notched front teeth. *Genital system.* Hypoplasia of descended testicles (1·5 × 1·0 × 0·7 cm. each). *External appearance.* Poorly developed boy; height 3 ft. 10 in.; weight 41 lb. 5 oz. P.M. No. 126/30. *Reg. No. 30339/30.

Case 11. (G. S.)* A boy, aged 17 years, was admitted under the care of Dr. Theodore Thompson. During the previous six months he had developed knock-knees. More recently he had been very thirsty. There was a history of nocturnal enuresis in childhood and he had been backward at school. A brother had died at the age of 2 years 6 months in Cleveland Street Hospital, the diagnosis being 'rickets and infantilism'. The mother was dead, the father and five other children were alive and well.

On examination he was a stunted youth, 4 ft. 7 in. in height and 5 st. 3 lb. 3 oz. in weight, with a pale puffy face; the skin was not abnormally dry. His mental condition was poor and he found reading difficult. There was no axillary or pubic hair; the beard area on the face was covered with a fine downy hair. The external genitalia were well developed; both testicles were descended and the penis was large for his size. There was slight prominence of the radial epiphyses at the wrists; 'beading' of costochondral junctions with slight degree of Harrison's sulcus; and prominent genu valgum with 8 in. separation of the internal malleoli when the knees were together. The brachial arteries were thickened. There was no enlargement of the heart. The blood-pressure was 120/80, and was once recorded as high as 130/100. The fundi were normal. Chvostek's and Trousseau's signs were negative. *Urine.* Pale; S. G. 1012; albumin, 1/8 volume. *Blood urea.* 0·09 per cent., rising to 0·33 per cent. in ten months; P. S. P., faint trace in each specimen; Urea concentration, 1·26 per cent. in 230 c.c. at second hour and 0·48 per cent. in 230 c.c. at third hour. *Serum calcium.* 7·4 mg. per cent.;

5·0 mg. per cent. ten months later. *Plasma phosphorus.* 3·5 mg. per cent.; 7·0 mg. per cent. ten months later. *Plasma phosphatase.* 1·03; 0·990. *Blood Wassermann.* Negative. *Blood count.* Red cells 4,500,000; haemoglobin 55 per cent.; colour index 0·61; white cells 6,280; polymorphs 68·5 per cent.; eosinophils 5·0 per cent.; small lymphocytes 16·5 per cent.; large lymphocytes 5·0 per cent.; large hyalines 4·5 per cent.; mast cells 0·5 per cent.

Radiological report on bones. Knee. Wide epiphyseal space; loss of definition at end of shaft and epiphysis; no definite 'wedging' of epiphysis; slight loss of density of bone shadow; bones smaller than control. *Skull.* Nothing abnormal; no obvious delay in eruption of teeth. *Wrist.* In addition to features seen in knee shows 'saucer' formation, especially at lower end of ulna; epiphyses of hand are also abnormal.

This patient was observed over a period of nearly ten months, at the end of which time he died in uraemia with fits.

Post mortem: Urinary system. Very small kidneys (right 5·2 × 3·0 × 2·0 cm., weight ¾ oz.; left 5·5 × 4·5 × 2·2 cm., weight 1¼ oz.) with somewhat adherent capsules; subcapsular surface partly raised, smooth and whitish yellow, partly somewhat depressed and coarsely granular, the granular part showing yellow-white nodules (up to 0·2 cm. diam.) in a somewhat sunken greyish-yellow ground. On cut surfaces: cortex shrunken; pattern destroyed; demarcation very indistinct, cortex and medulla being both almost uniformly pale yellowish white, faintly and irregularly flecked with grey and yellow; very great narrowing of kidney substance at poles of kidneys (down to 1·0 cm. deep); unusual width of left kidney, possibly due to regeneration in convex border and upper pole; no prominence of vessels. Dilatation of pelves (left 3·5 × 2·0 cm.; right 2·2 × 2·0 cm.). Dilatation of left ureter (1·9 cm. circumf.) and slight dilatation of right ureter (1·4 cm. circumf.). Great dilatation of bladder (17·0 cm. circumf.). *Heart.* Slight hypertrophy of left ventricle (R. V. 0·2 cm., L. V. 0·8 cm.; weight 7¾ oz.). *Skeleton.* Extreme genu valgum. Deep zone of proliferation of cartilage in ribs (2·0 mm.), upper end of humerus towards shaft (2·0 mm.), head of femur towards neck (2·0 mm.), great trochanter (to 1·5 mm.), lower end of femur towards shaft (inner condyle 2·5 mm., outer condyle 5·0 mm.), upper end of fibula (2·5 mm.), lower end of fibula towards shaft (3·0 mm.), and lower end of radius towards shaft (1·5 to 4·0 mm.). Narrow line of white, resting, cartilage towards epiphyses. Zone of osteoid metaphysis (1·0 to 2·0 mm.) in ribs. Narrow zone of osteoid tissue beneath head of humerus. No zones of provisional chondral calcification. Projection of zones of proliferated cartilage and osteoid tissue of ribs towards thoracic cavity. Slight depression of head of femur. Long internal condyle, articular surface of lower end of femur at an angle of 35° to horizontal. Fontanelles closed; skull sutures not united. *Genital system.* Testicles small; tubules apparently well developed. *External appearance.* Dwarf, with extreme genu valgum (internal malleoli 23 cm. apart); height 4 ft. 7 in.; weight 72 lb. 6 oz. P.M. No. 268/30. *Reg. No. 31302/29.

Case 12. (J. W.)* A man, aged 26 years, was admitted under the care of Dr. Donald Hunter. He had been unwell for about two years, complaining of shortness of breath, headaches, and failing vision; more recently he had noticed he was very thirsty and he had had nocturnal frequency. His urine became darker than normal about three weeks before admission. For the past three years his occupation had been that of an ice-cream vendor; before

that he had worked at first in a wall-paper factory, and secondly in a coach-painting business, during which time lead colic had occurred among his fellow workmen. He had been employed at each of these jobs for from two to three years. He had had scarlet fever at the age of 13, but there was no record of any renal complication. He had been 'weak from birth', and his mother said that he had had all the childish ailments. His mother was said to have 'high blood-pressure' and a brother had died of Bright's disease at the age of 21 years. He had shaved only twice in his life.

On examination he was a pale youth with moderate anaemia of mucous membranes and a 'muddy complexion', 5 ft. 7 in. in height. There was a little fine hair on the upper lip and chin; the axillary hair was very scanty; the pubic hair was less than normal; the trunk and extremities were completely devoid of hair. The penis and testicles were small, but erection occurred normally. There was marked kyphosis, and a slight degree of genu valgum, causing 2½ in. separation of the internal malleoli when the knees were together. The teeth were small and worn. No blue line was evident. The radial arteries were thickened. The heart was definitely enlarged, the apex being ½ in. external to the nipple line. The blood-pressure was 230/140. Examination of the fundi revealed very marked swelling of the discs, numerous areas of haemorrhage and exudate, with a well marked macular fan. Chvostek's and Trousseau's signs were negative. *Urine.* Blood visible to the naked eye was present for the first few days; afterwards the urine was clear and pale; albumin, ¼ to 1/10 volume; S.G. 1010; deposit, a few hyaline casts, blood and epithelial cells; culture, *Staphylococcus albus.* Polyuria to 119 oz. in twenty-four hours. A seven-day specimen revealed a slight trace of lead. *Blood urea.* 0·112 per cent., rising to 0·396 per cent., during the period of seven months he was under observation; P.S.P., a trace in three hours; urea concentration, 0·87 per cent. in 223 c.c. at third hour. *Serum calcium* not estimated. *Blood count.* Red cells 4,800,000; haemoglobin 78 per cent.; colour index 0·81; leucocytes 6,400. Six months later: Red cells 3,300,000; haemoglobin 45 per cent.; colour index 0·68; white cells 6,000. *Blood Wassermann test.* Negative.

This patient died in uraemia seven months after he first came under observation. There were no fits, and Chvostek's and Trousseau's signs were negative throughout the illness.

Post mortem: Urinary system. Kidneys (3¾ oz.); hydronephrosis of left kidney; great destruction of left kidney with dilatation of its pelvis and calyces, the renal tissue being reduced to a thin tough pink membrane (from 0·1 to 0·25 cm. thick), the pelvis being 6·0 cm. in circumference; great haemorrhage in pelvis around the ureteric orifice. Slight hydronephrosis of right kidney (pelvis 5·0 cm. circumf.) slight dilatation of calyces and a few haemorrhages in the renal pelvis; pale yellowish-grey contracted cortex (cortex/medulla as 0·25/9) with smooth glistening patternless cut surface, wavy demarcation, and considerable blurring of pattern in pale grey-brown medulla; slight prominence of arteries; focal areas of greater contraction and fibrosis of cortex, and in places, of both cortex and medulla; very ill-defined nodules (0·6 cm. diam.) of regeneration in cortex. No obstruction in slightly dilated left ureter (1·1 cm. circumf.); no obstruction in slightly dilated right ureter (1·1 cm. circumf.). Dilatation (20·0 cm. circumf.), slight hypertrophy (0·4 cm. thick), and thickening of trabeculae of bladder. *Heart.* Considerable hypertrophy, without dilatation, of left ventricle (L.V. 1·5, R.V. 0·4 cm. thick) (weight 16¼ oz.). *Skeleton: Ribs.* The third right and

sixth left ribs showed no recognizable abnormality on section. The marrow was finely mottled with red and yellow. *Right femur.* The forward bow below the trochanters was very slightly greater than in a control. The corticalis was 1·1 cm. thick and resembled ivory. In the neck, 1·8 cm. below the upper border and immediately in front of the anterior limit of the great trochanter was a slaty-grey area (0·2 cm. diam.) which suggested cartilage. Rich red marrow filled half the head, all the neck, and the upper 14 cm. of the shaft, which was 33 cm. long; similar marrow lay in large areas in the next 5 cm. and formed a zone beneath the corticalis throughout the rest of the shaft. *Left tibia.* The epiphysis was completely united to the shaft, but could be recognized by its closer texture. The marrow was fatty. *Nervous system.* Layer of recent clot (up to 0·5 cm. thick) amounting to about one ounce, on inner surface of dura of left cerebral hemisphere; similar clot infiltrating lepto-meninges of cisternae pontis and basalis, left Sylvian fissure and the surface of the convolutions about the Sylvian fissure; bleeding point not found. A little blood found in meninges of spinal cord. No other abnormality seen in cord. *External appearance.* Pallid wasted man; height 5 ft. $5\frac{1}{2}$ in.; weight 104 lb. P.M. No. 470/30. *Reg. No. 30516/30.

Case 13. (R. P.)* A girl, aged 8 years, was admitted under the care of Dr. Theodore Thompson. As a child she had always been delicate. For three months she had been out of sorts and the mother had thought that the child was not gaining weight. A week before admission she had begun to complain of abdominal pain and vomiting; her face had been slightly puffy; and on the day before admission the urine had been red. There had been no nocturnal enuresis, frequency, or painful micturition.

On examination she was a moderately well developed child, 3 ft. 9 in. in height. The skin was pale and dry, and there was marked anaemia of the mucous membranes. There were no obvious rickety bone changes. The radial and brachial arteries were slightly thickened. The heart was not enlarged. The blood-pressure was 150/70 to 120/65. There was just demonstrable pitting oedema in the lumbar region and over the shins. No abnormality was seen in the fundi. *Urine.* Naked-eye blood and much pus; S. G. 1010–12; albumin, $\frac{1}{4}$–$\frac{3}{4}$ volume; culture, paracolon bacilli. *Blood urea.* 0·248 per cent.; P. S. P., 2·8 per cent. in two hours; urea clearance, 10 per cent. of normal. *Blood count.* Red cells 2,800,000; haemoglobin 44 per cent.; colour index 0·78; white cells 13,600, with 85·5 per cent. of polymorphs. *Serum calcium.* 8·7 mg. per cent. *Radiological examination of urinary tract.* Negative. *Radiological examination of bones.* 'The only doubtful epiphysis is the A. P. view of the right wrist. In the lateral view nothing abnormal is seen.'

This patient died in uraemia six weeks after admission.

Post mortem: Urinary system. Left kidney (7·0 × 3·0 × 3·0 cm.) with surface consisting of raised nodules (up to 3·0 cm. diam.) mainly smooth and creamy white, a few mottled with green and red, and stippled with raised yellow dots; nodules separated by sunken bands (up to 0·7 cm. wide), some smooth, but the majority showing yellow granular stippling; abscess (0·2 cm. diam.) on anterior surface of lower pole, partly in substance, partly protruding; a few petechiae on surface; cut surface showing regeneration nodules (up to 4·0 × 2·5 cm.), some creamy white and structureless, largest faintly mottled with opaque yellow lipoid flecks and grey pin-head areas; a few petechiae in substance; very little medulla remaining, one pyramid only recognizable

in each pole. Dilatation of calyces and pelvis; double pelvis and ureter (upper ureter 0·9 cm., lower 1·5 cm. circumf.). Very small right kidney (4·0 × 2·0 × 1·5 cm.) with faintly granular pinkish-yellow and grey subcapsular surface showing two raised smooth paler nodules (larger 1·0 cm. diam.). A few petechiae in surface; greater part of cut surface showing finely granular yellowish-grey cortex very poorly demarcated from grey medulla; two creamy white regeneration nodules corresponding to those on surface. A few petechiae in substance and in mucosa of dilated pelvis. Dilatation of ureter (1·2 cm. circumf.). Dilatation of bladder (12·5 cm. circumf.) with slight hypertrophy (wall 0·4 cm. thick); slightly injected bladder mucosa. Left kidney 2 oz., right kidney ½ oz. *Heart.* Hypertrophy of left ventricle (R. V. 0·25, L. V. 1·0 cm.), 4¼ oz. *Skeleton.* No rickets in ribs or femur. *Nervous system.* Numerous small petechiae in pons. *External appearance.* Moderately nourished and developed girl; height 3 ft. 9 in.; weight 34 lb. 14 oz. P.M. No. 541/31. *Reg. No. 41610/31.

Case 14. (B. L.)* A girl, aged 17 years, was admitted under the care of Professor Ellis. She had been always small for her age, pale, and puffy under the eyes. Three years ago she had begun to notice that she tired very easily and that her legs felt weak. From this time she had hardly grown at all. For six months she had had an aching pain in the left loin and had seemed to walk awkwardly; two months before admission she had begun to complain of headaches, and there had been vomiting and epistaxis. There had been no frequency, nycturia, or haematuria. Her periods had always been scanty, usually lasting for one day. As a child she had had nocturnal enuresis. She had had scarlet fever in childhood, but no details were available. Her parents, two brothers, and a sister were quite well and of normal size.

On examination she was a small girl, 4 ft. 9 in. in height, with dry, coarse skin of an earthy-yellowish tint. Her face was slightly puffy round the eyes, and there was anaemia of the mucous membranes. The secondary sexual characteristics were normally developed. There was slight 'beading' of the costochondral junctions and slight bowing of the legs, especially in the lower third of the tibiae. The brachial arteries were definitely thickened. There was no enlargement of the heart. Hypertension was observed on admission, the blood-pressure being 145/110, but later the readings varied between 115/80 and 125/90. There was no demonstrable oedema. The fundi were normal and no changes were detected in the lenses. The teeth were normal. *Urine.* Pale; S. G. 1008–15; albumin, a cloud; deposit, a few leucocytes and red cells; culture, sterile. *Blood urea.* 0·178 per cent.; P. S. P., trace in two hours; urea clearance, 8·6 per cent. of normal. *Serum calcium.* 6·3 mg. to 5·4 mg. per cent. over a period of three months. *Plasma phosphorus.* 8·75 mg. to 9·0 mg. per cent. over a period of three months. *Blood Wassermann test.* Negative. *Blood count.* Red cells 3,000,000; haemoglobin 45 per cent.; colour index 0·75; white cells 7,200; polymorphs 71·5 per cent.

Radiological examination. Bones. Skull normal; hips, delay in union of pelvic bones; knee, bones small; ankles and wrists, no definite delay in union. Fusion appears a little slow throughout.

Pyelography. Slight dilatation of right ureter, but no flattening of calyces; left ureter is too large for the size and age of the patient, and there is flattening of the upper calyces.

This patient was in hospital for seven weeks, at the end of which time she

was sent home. Two weeks later she was readmitted, complaining of severe pain in the left hip; radiological examination proved this to be due to a fracture of the neck of the left femur. The same night she had a fit and fractured the neck of the right femur. She died in uraemia nine days later.

Post mortem: Urinary system. Very small kidneys (right 5·0 × 2·0 × 1·8 cm.; left 6·3 × 3·0 × 1·5 cm.); on cut surface great destruction of substance (maximum thickness 1·0 cm.); cortex and medulla indistinguishable; substance yellowish-grey, occasionally pink and showing groups (up to 0·8 × 0·4 cm.) of minute lipoid flecks; outer surface finely granular with a few raised nodules (up to 1·2 cm.), corresponding to lipoid flecked areas. Great dilatation of pelves (right 4·5 cm. long and 2·5 cm. circumf.; left 5·0 cm. long and 3·0 circumf.); dilatation of calyces and great flattening of pyramids; dilatation of ureters (right 1·3 cm., left 1·4 cm. circumf.). Hypertrophy and great dilatation of bladder (18·0 cm. circumf., wall 0·4 cm. thick); slightly granular mucosa of trigone; slight injection of mucosa of bladder; foul-smelling urine with thick granular yellowish-white deposit in bladder. (Kidneys not weighed, complete specimen with ureters and bladder.) *Heart.* Moderate hypertrophy (R.V. 0·3 cm., L.V. 1·2 cm.; weight 8¼ oz.). *Skeleton.* Ribs pliable and easily cut with knife; zone of provisional chondral calcification interrupted. Body of thoracic vertebrae cut with knife. Very close spongy texture in all bones. Cartilaginous junctions between manubrium and sternum, one in mesosternum, below head of humerus, below head and above condyles of femur. No visible junction in descending ramus of pubis. Fracture through necks of both femora. No deformities of bone. Pale pink marrow in sternum, ribs, vertebrae, neck, and shaft of humerus, throughout upper 19 cm. of 27 cm. shaft of femur and in periphery of rest of shaft. *Nervous system.* Petechiae in splenium of corpus callosum; oedema of brain. A little subarachnoid haemorrhage over cervical and thoracic regions of spinal cord. No other abnormalities in cord.

External appearance. Well developed breasts; abundant axillary and pubic hair; small well-nourished girl; height 4 ft. 8 in.; weight 79 lb. 4 oz. P.M. No. 54/32. *Reg. No. 41795/31.

Case 15. (W. P.)* A boy, aged 19 years, was admitted under the care of Mr. Milne. He complained of difficulty in walking, with pain in both knees and feet. Some years previously he had been in Poplar Hospital for a period of seven weeks. His parents, three brothers, and three sisters were alive and well.

On examination he was a thin, sallow youth. The axillary and pubic hair was very scanty. The external genitalia were well developed. There was marked 'bossing' of the frontal bones. The epiphyses at the wrists, knees, and ankles were enlarged. Both femora showed a curving with the convexity antero-externally. There was no enlargement of the heart. The blood-pressure was 120/60. *Urine.* Pale; S. G. 1008; albumin, 1/3 volume; deposit, pus and epithelial cells. *Blood urea.* 0·121 per cent.; P. S. P., a trace in three hours; urea concentration 0·66 per cent. in 115 c.c. at second hour and 0·63 per cent. in 204 c.c. in third hour. *Serum calcium.* 8·0 mg. per cent. *Plasma phosphorus.* 4·0 mg. per cent.

The fate of this case is unknown. *Reg. No. 12201/28.

Case 16. (C. P.)* A boy, aged 15 years, was admitted under the care of Professor Ellis. He was very small at birth, began to talk at the age of 2 years, and began to walk, in a waddling fashion, when he was 3 years old.

Between the ages of 4 and 5 years his knees began to bend and he complained of thirst. At the age of 8 years he had an operation to straighten his legs (? osteotomy). Eighteen months later, when he attempted to begin to walk again, his legs became deformed once more. These deformities, together with a bending above the wrists, gradually became more marked. One year before admission he fell from a height of about 3 ft. and fractured his right femur; union was reported good and firm in six weeks. He had always suffered from polyuria and nocturnal enuresis. He had not been to school since he was 6 years old, when he was considered very backward. His parents and two brothers were alive and well.

On examination he was a grossly deformed emaciated dwarf, 3 ft. 6 in. in height and 2 st. 12 lb. 12. oz. in weight. The mentality was that of a child half his age. He could write poorly to dictation, made childish drawings, and was unable to do sums. The voice was highly pitched. The head was rather square ($21\frac{3}{8}$ in. circumf.) with well marked frontal 'bossing' and a bulging occiput; the fontanelles were closed; there was marked prominence of the superior maxillae on either side of a 'snub' nose, the bridge of which was sunken; the malar bones had the appearance of having been pushed forwards. The chest had a circumference of 21 in. at the level of the nipples, and showed bilateral Harrison's sulcus, excessive curvature of both clavicles, and marked thickening of the costochondral junctions. In the upper limbs there was a slight bowing of the right humerus; a gross bending deformity towards the ulnar side just above both wrists, the left at 90° and the right at about 60°; the epiphyses were moderately enlarged, especially at the wrists; and the fingers were short and stubby, with very short and sunken nails. The spine was scoliotic, with a thoracic curve to the right and a lumbar curve to the left; the sacrum was prominent, and the iliac crests were rather splayed out. In the lower limbs there was gross genu valgum, with an external dislocation of the patella on the right side; the femora were curved with the convexity antero-externally; the right tibia and fibula were straight, but the left showed a gross varus deformity just above the ankle, so that the external malleolus and outer border of the foot rested on the ground; there was marked talipes equinus on the right side; and the epiphyses at the knees and ankles were enlarged. The joints showed marked limitation of movement with the exception of the left ankle, which had a flail-like movement. The skin was dry and of a uniform pale brownish colour; the hair on the head was normal, the eyebrows were thin, and there was no axillary, pubic, or body hair. The penis and testicles were small. There was moderate anaemia of the mucous membranes. The eyes were blue with white sclerotics. The superficial arteries were remarkably thickened, and the radial arteries could easily be rolled under the fingers. There was no cardiac enlargement; the blood-pressure was 115/65. The abdomen was somewhat distended, but there was no evidence of ascites. Mr. Sprawson reported that 'macroscopically the teeth appeared normal as regards calcification'. Chvostek's and Trousseau's signs were negative. The fundi were normal. *Urine.* Pale; S. G. 1006–10; albumin, a heavy cloud; deposit, leucocytes and epithelial cells. *Blood urea.* 0·153 per cent.; P. S. P., a trace in two hours; urea clearance, 10 per cent. of normal. *Blood count.* Red cells 4,700,000; haemoglobin 72 per cent; colour index 0·76; white cells 3,600. *Blood Wassermann test.* Negative. *Serum calcium.* 8·6 mg. per cent. *Plasma phosphorus.* 5·8 mg. per cent. *Plasma phosphatase.* 0·940.

This patient died in uraemia shortly after leaving hospital. There was no necropsy. *Reg. No. 31719/30.

Case 17. (A. N.)* A boy, aged 4 years, was admitted under the care of Dr. Maitland-Jones. He had been born at full term, weighing 8½ lb. at birth, and had been breast-fed for fourteen months. The first tooth had appeared at 9 months, and he had begun to walk at 16 months. Nothing abnormal had been noticed until the age of 2 years, when he had begun to drink excessively, even 'sucking pickles for juice'. There was polyuria with occasional enuresis at this time. Since then he had failed to grow, but, apart from occasional vomits, the general health had been good. He had been circumcised when he was 2 years old. The parents and one sister were alive and well.

On examination he was a small active boy 32 in. in height and 24 lb. 14 oz. in weight; he looked about two years old. The cheeks were highly coloured, but the remainder of the skin was dry and of a greyish-yellow colour. There was no marked anaemia. No obvious rachitic deformities were present, and the anterior fontanelle was closed. There was no arterial thickening and no cardiac enlargement. The blood-pressure was 105/75 to 110/80. The abdomen was protuberant, but no ascites or enlargement of organs was demonstrable. Examination of the fundi revealed no abnormality. The external urinary meatus appeared normal. *Urine.* Pale; S. G. 1007–10; albumin, a heavy cloud; deposit, occasional red cells and leucocytes. *Blood urea.* 0·073 per cent.; P. S. P. and urea concentration, 2·6 and 0·63 per cent. in 70 c.c. at second hour, and 3·3 and 0·66 per cent. in 90 c.c. at third hour. *Blood Wassermann test.* Negative. *Blood count.* Red cells 5,700,000; haemoglobin 84 per cent.; colour index 0·73; white cells 24,000; polymorphs 51 per cent.; eosinophils 9·5 per cent.; small lymphocytes 24 per cent.; large lymphocytes 10 per cent.; large hyalines 5·5 per cent. *Serum calcium.* 8·5 mg. per cent. *Plasma phosphorus.* 4·3 mg. per cent. *Plasma phosphatase.* 19·3 units per 100 c.c.

Radiological examinations. Hands. Delay in appearance of centre for cuneiform. *Wrists.* Splaying and some 'cupping' of metaphysis of radius and ulna. *Fibula* and *tibia.* Flattening of juxta epiphyseal lines at upper and lower extremities of both bones. No widening of actual epiphyses seen at any point. *Skull.* The pituitary fossa was a little deep but probably within normal limits. *Bladder.* Cystogram showed a somewhat distended bladder, but there was no abnormality of shape and no reflux into the ureters.

This case was in hospital for five weeks with irregular fever up to 102°. Death preceded by convulsions occurred three weeks after discharge. There was no autopsy. The fever and leucocytosis were unexplained. The absence of anaemia was unusual. *Reg. No. 30281/32.

Case 18. (D. R.)* A male child, aged 22 months, was admitted under the care of Professor Ellis. He was the second child of an unmarried mother, the first, aged 14 years, being alive and well. The mother was said to have had kidney trouble for eight years and to have been in bed for five months during her second pregnancy on account of her kidneys. The child had been born at the eighth month and had weighed 3 lb. 12 oz. at birth. Both feet had been noticed to be deformed at birth. When two to three weeks old he had been taken to Vincent Square Infants' Hospital, where he had remained for four months. At the age of 11 months he had been given to a foster mother who had fed him on 'Slippery Elm' food. Shortly after this he had begun to vomit, and eventually, at the age of 17 months, he had

been admitted to the Hospital for Sick Children, Great Ormond Street, because of persistent vomiting and failure to grow.

On examination he was a very small infant weighing only 12 lb. 2 oz. The skin was dry and of a yellowish-grey colour. The sclerotics were bluish. In the skull there was marked ' bossing ' of the frontal bones and the anterior fontanelle was open and pulsating. There was a lower dorsal kyphosis. The costochondral junctions were enlarged, giving rise to obvious ' beading ', but there was no obvious enlargement of the epiphyses at the wrists. The legs showed slight bilateral genu varum and bilateral talipes equino-varus. There were four upper and two lower incisors erupted. There was no thickening of the arteries. The heart was not enlarged. The blood-pressure was 100/40. There was no abnormality detected in the lungs or abdomen. The external genitalia appeared normal. *Urine.* Albumin, a heavy cloud; deposit, few leucocytes and red cells, epithelial cells; culture, paracolon bacilli. *Blood count.* Red cells 2,400,000; haemoglobin 32 per cent.; colour index 0·86; white cells 3,500. *Blood urea.* 0·177 per cent. *Serum calcium.* 9·8 mg. per cent. *Plasma phosphorus.* 3·5 mg. per cent. *Plasma chlorides.* 0·60 grm. per 100 c.c. (as NaCl). *Plasma phosphatase.* 25·3 units per 100 c.c.

Radiological examinations. Skull. The only doubtful point was the sella, which appeared to project forward under the clinoid process more than normal. The *hands* were small with delayed epiphyses. The *right femur* showed slight coxa vara; the *left femur* showed marked coxa vara with a ' slipped epiphysis ', and the whole of its upper end was less well developed than the rest of the bone. The *tibiae* and *fibulae* showed deformities at the upper and lower ends of the shafts with loss of outline at the epiphyseal lines; also bending of the shafts. The *feet* were small with delay in the appearance of the epiphyses of the phalanges and metatarsals.

The ultimate fate of this case is unknown. *Reg, No. 30239/32.

Case 19. (R. F.)* A boy aged 18 years was admitted under the care of Professor Ellis. He had been perfectly well until he was 9 years old when he had begun to lose control over his water; there had been a more or less continuous dribble during the day and night. This state of affairs had continued for nearly seven years when he had had an attack of severe pain in the right loin; there had been vomiting, but no pain or frequency of micturition and no haematuria. Two years before admission he had been an in-patient in St. Andrew's Hospital, Bow, where the urine was found to contain albumin, pus, and blood; an X-ray examination showed no evidence of calculus. On discharge, two months later, his pain and incontinence had completely disappeared. He had then remained well, but had noticed that his legs were weak, and later that they began to bend. This had gradually increased and had caused him to seek advice from the orthopaedic department. He had always been thirsty for ' as long as I can remember '. There had been no nocturnal frequency. He had not had scarlet fever. His parents, six brothers, and three sisters were alive and well.

On examination he was a tall, thin, sallow youth, 5 ft. 10 in. in height and 9 st. in weight. The skin was dry and of a yellowish-grey tint. There was anaemia of the mucous membranes. The bony deformities present were marked ' rickety rosary ', enlarged epiphyses at the wrists, and marked genu valgum, more especially on the right side, causing 8½ in. separation of the internal malleoli. The facial hair was fine and rather scanty; there was little on the limbs; axillary and pubic hair were present, the

latter being of female distribution. The external genitalia were well developed. There was slight thickening of the radial and brachial arteries. The heart was not enlarged. The blood-pressure was 120/80. The fundi revealed no abnormality. There was no oedema. Chvostek's sign was positive; Trousseau's sign was negative. This patient is still alive and able to carry on with his work. *Urine.* Pale; S. G. 1010; albumin, a heavy cloud; deposit, many red cells, few leucocytes and epithelial cells; culture, *Staphylococcus albus. Blood urea.* 0·075 per cent.; P. S. P., a trace in two hours; urea clearance, 50 per cent. of normal. *Blood count.* Red cells 4,700,000; haemoglobin 65 per cent.; colour index 0·69; white cells 6,000; polymorphs 70 per cent. *Blood Wassermann test.* Negative. *Serum calcium.* 6·75 mg. per cent. *Plasma phosphorus.* 5·1 mg. per cent. *Plasma phosphatase.* 0·660.

Radiological examination. Genu valgum is present in both knees and is worse on the right side. There is a certain amount of splaying out of the diaphysis, especially on the right side. Delayed calcification of the epiphyseal lines is present; they are wider than normal, especially in the right femur where they show waviness.

Pyelography. Ureteric catheterization by Mr. Dix. On cystoscopic examination the site of the ureteric orifices was below and not on the muscular bar, and the orifices were widely dilated.

A cystogram showed marked dilatation with diverticulosis of the bladder. The uppermost point reached very high, the whole shape was unusual, and much bigger than normal. No ureteric reflux. *Right pyelogram.* Hydronephrosis; the pelvis of the kidney is about four times the normal size; and the ureter very dilated. *Left pyelogram.* Hydronephrosis with enormously dilated ureter. *Reg. No. 31050/32.

Case 20. (B. M.)* A girl aged 6 years was admitted under the care of Mr. Milne. She had had rickets when a baby, and at the age of 9 months had only weighed 8½ lb. The rickets had caused bowing of her legs, as a result of this she did not walk unaided until 4 years old. She had often complained of great thirst. Ever since infancy she had had to get up at night to pass water; usually she had to void only once during the night, but then 'does enough for three times of an ordinary person'. During this first admission the urine contained a trace of albumin and pus, and culture grew *B. coli.* Bilateral Gant's subtrochanteric osteotomy was performed. The operation was successful, and for two years she carried on quite well, even being able to skip.

Three years after the first admission, i.e. when she was 9, she was readmitted because her legs were again getting crooked. She was said to be undersized and under-developed. *Urine.* S. G. 1002; albumin, a cloud. *Blood urea.* 0·09 per cent., with impaired P. S. P. excretion and urea concentration. The blood-pressure was noted as 110 systolic. Radiological examination revealed changes typical of healing rickets in all epiphyseal regions. The blood calcium and inorganic phosphorus were recorded as 9·9 and 3·53 mg. per cent. A year later, when she was 10 years old, bilateral Macewen's osteotomy was performed. At this time the blood urea was recorded as 0·09 per cent. At the age of 11 years she was admitted again for reinvestigation.

On examination she was a small intelligent child, 3 ft. 6½ in. in height, with a smooth pale freckled skin. The skin was not abnormally dry and there was no discoloration. The hair on the scalp was fine and silky; there

was no pubic, axillary, or body hair. Her head was small, 19 in. in circumference; there was no 'bossing' of the frontal bones. There was no 'rickety rosary' or other deformity of the chest. The epiphyses at the wrists were enlarged and there was prominent genu valgum. There was definite thickening of the brachial and radial arteries. The heart was not enlarged. The blood-pressure was 95/50. The fundi were normal. Chvostek's and Trousseau's signs were negative. *Urine.* Pale; S. G. 1010; albumin, a cloud. *Blood urea.* 0·09 per cent.; P. S. P., 14·8 per cent. in two hours; urea concentration, 0·66 per cent. in 112 c.c. at second hour and 0·78 per cent. in 53 c.c. at third hour. *Blood Wassermann test.* Negative. *Blood count.* Red cells 4,500,000; haemoglobin 62 per cent.; colour index 0·68; white cells 8,840.

Two years later, when she was 13 years old, the following observations were made. Very bright and intelligent; height 4 ft. 1½ in.; B. P. 105/65. *Blood urea.* 0·13 per cent. *Blood count.* Red cells 5,200,000; haemoglobin 72 per cent.; colour index 0·72; white cells 10,000; polymorphs 67 per cent. *Platelets* 260,000; bleeding time 1 min. 35 secs.; coagulation time 2 mins. 15 secs. *Serum calcium.* 9·7–10·5 mg. per cent. *Plasma phosphorus.* 4·3–5·0 mg. per cent. *Plasma phosphatase.* 0·600–·946.

At the present time she is well, but still has polyuria and marked thirst. For the last four years she has been at a special school for delicate children. She has hardly grown at all during the past year. She is now aged 14. Her periods began three months ago and have been regular.

On examination she is bright and intelligent. There is no discoloration of the skin, nor is there any evidence of anaemia. The breasts are well developed; axillary and pubic hair is beginning to appear. The skull is slightly square, but there is no pronounced bossing of the frontal or parietal bones. There is a definite kyphosis in the upper, and a slight scoliosis to the right in the lower dorsal vertebrae. The epiphyses at the wrists and at the first interphalangeal joints of the middle and ring fingers are enlarged. There is well marked genu valgum with 4 in. separation of the internal malleoli when the knees are together; and slight outward bowing of the left tibia in its lower part. The teeth are well formed and in good condition. The brachial arteries are easily palpable. The heart is not enlarged, the apex being 3¼ in. from the midline; the blood-pressure is 95/55. There is no distension of the abdomen; the kidneys are not palpable. There is no oedema. The fundi are normal. Chvostek's and Trousseau's signs are negative. *Urine.* Albumin, a cloud; deposit, a few leucocytes and red cells; culture, *Staphylococcus albus. Blood urea.* 0·103 per cent. *Serum calcium.* 7·6 mg. per cent. *Plasma phosphorus.* 3·9 mg. per cent.

A *cystogram* showed very considerable enlargement of the bladder, with a wide prolongation upwards and to the right, probably due to a diverticulum. *Reg. No. 20787/34.

Our acknowledgements are due to Professor H. M. Turnbull for permission to use the records of naked-eye appearances at necropsies, to the Physicians and Surgeons of the Hospital who have given us access to their cases, and to the Directors of the Clinical Laboratory and the Radiological Department for the results of examinations conducted in their Departments. We should like also to acknowledge our indebtedness to Dr. Donald Paterson who kindly sent us Case 18 of this series.

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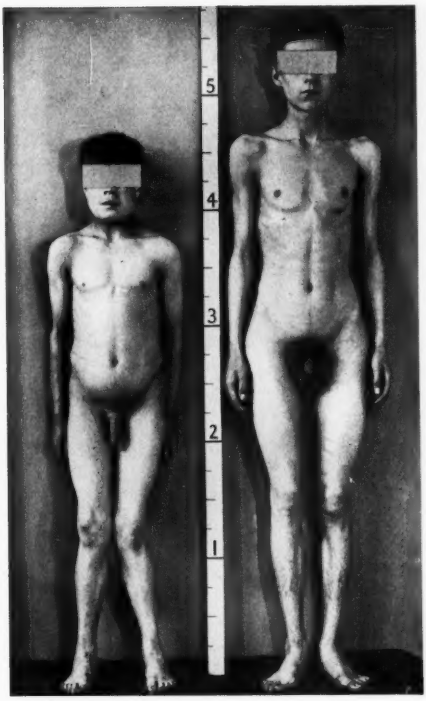
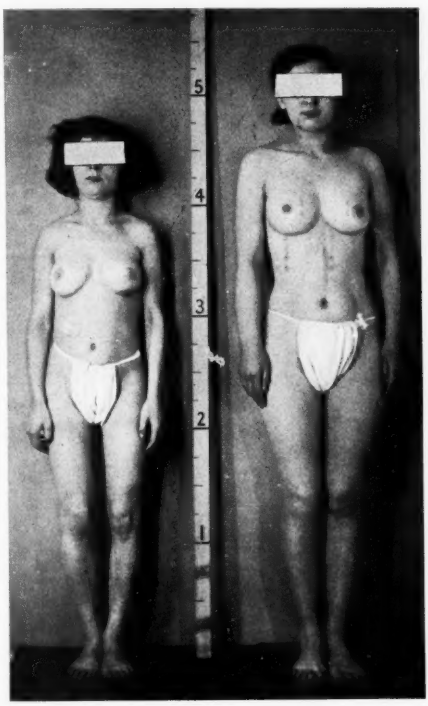
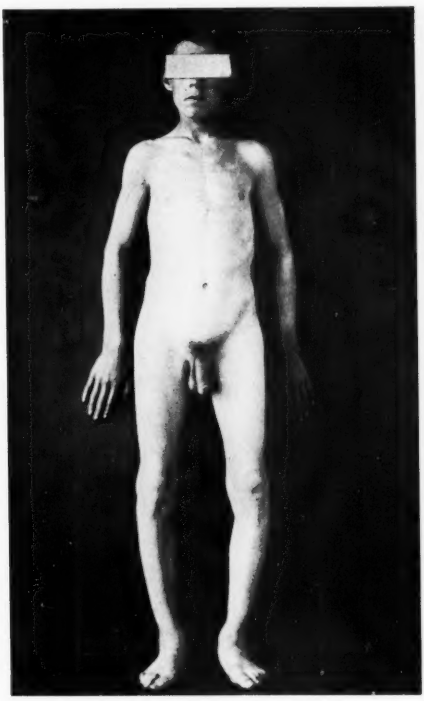
Renal dwarfism. Case 6 (A.B.), aged 9 years



Renal dwarfism. Case 11 (G.S.), aged 17 years. (Normal control, same age)



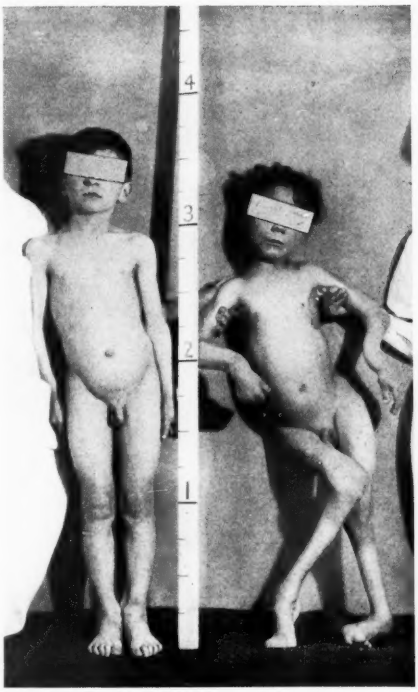
Renal dwarfism. Case 14 (B.L.), aged 17 years. (Normal control, same age)



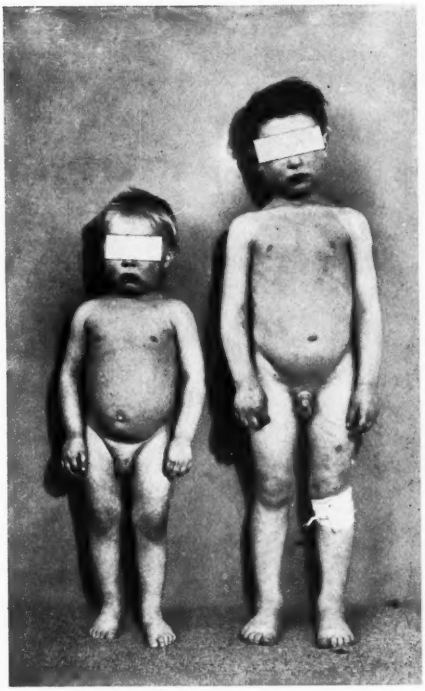
Renal rickets. Case 15 (W.P.), aged 19 years

Case 14 (B.L.). Right pyelogram showing, dilatation of pelvis and ureter

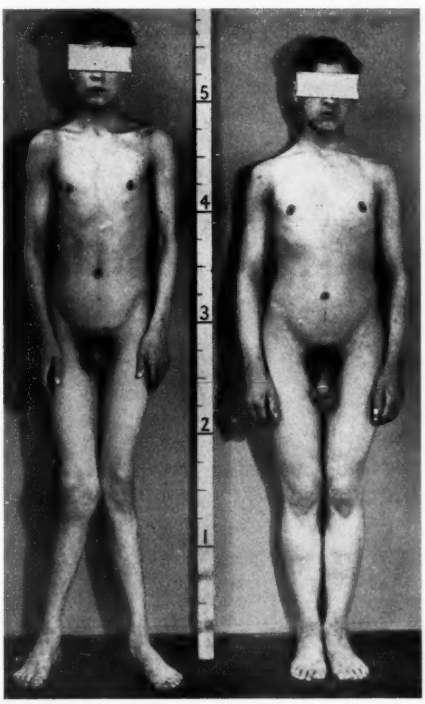
Case 14 (B.L.). Left pyelogram, showing dilatation of pelvis and ureter



Renal dwarfism. Case 16 (C.P.), aged 15 years. (Normal control, aged 8)

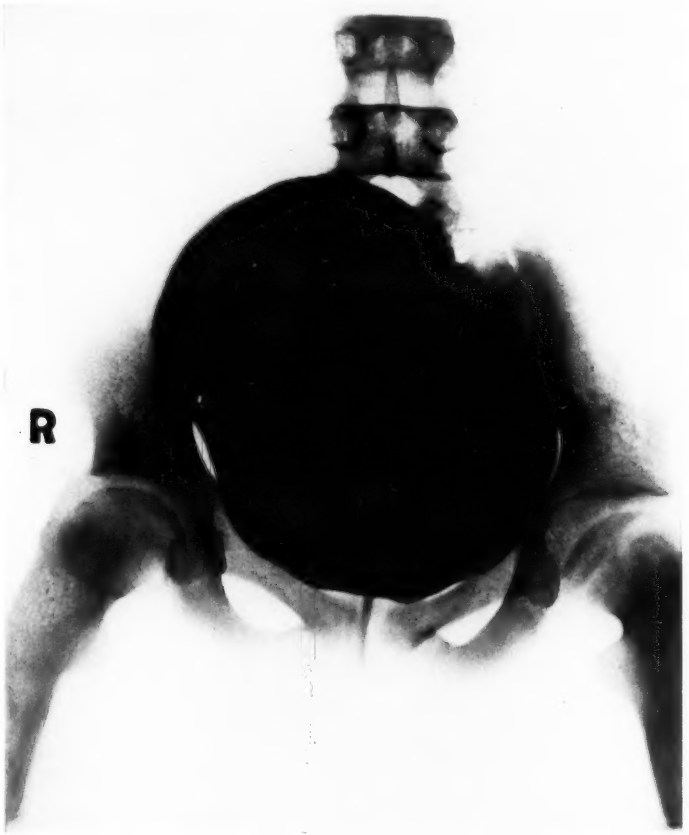


Renal dwarfism. Case 17 (A.M.), aged 4 years. (Normal control, same age)

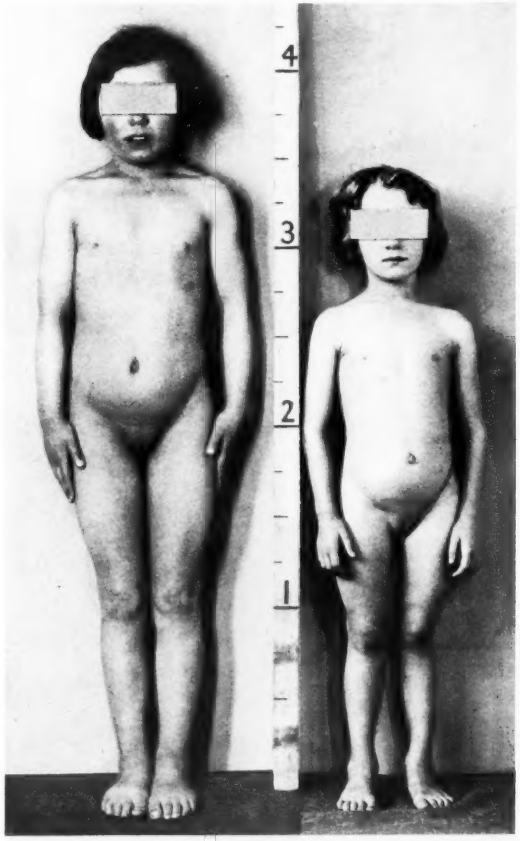


Renal rickets. Case 19 (R.F.), aged 18 years. (Normal control, same age)

Case 19 (R.F.). Cystogram, showing dilatation of bladder



Case 20 (B.M.). Cystogram, showing dilatation of bladder



Renal dwarfism. Case 20 (B.M.), aged 11 years.
(Control, same age)

616.919
616.008.816

PRECIPITIN REACTIONS IN THE BLOOD OF RHEUMATIC PATIENTS FOLLOWING ACUTE THROAT INFECTIONS[1]

By BERNARD SCHLESINGER and A. GORDON SIGNY
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In a former research on the relationship of throat infection to acute rheumatism in childhood (1), a 'silent period' of ten to twenty-one days was repeatedly noticed to intervene between rheumatic lapses and the tonsillitis, or pharyngitis, which almost invariably preceded them. This observation has since been confirmed by others (2) (3) (4), and offers a new line of inquiry into the pathogenesis of acute rheumatism. The 'silent period' has earned its name from the fact that during that time the patient, after recovering from his throat infection, feels perfectly well, his temperature is normal, and there is no outward indication of the brewing storm of acute rheumatic fever with severe and often fatal pericarditis. This apparent well-being, however, does not preclude the possibility that meanwhile certain reactions are taking place in the patient's defence mechanism which might be demonstrable in his blood-serum. These are probably manifold, and as a preliminary investigation during the past year we have concentrated on the precipitin reaction, as this is not attended by too many technical difficulties in its demonstration.

The Precipitin Test

Since Kraus's original observation in 1897, that antisera, prepared against certain bacteria, gave rise to specific precipitation when mixed with a bacteria-free filtrate of a broth culture of the homologous organism, the test has received a wider application in the hands of numerous other observers.

The discovery that not only bacteria, but any foreign protein of sufficient chemical complexity, will stimulate the production of these antibodies when introduced parentally into the animal tissues has, for instance, proved of considerable medico-legal importance in determining the human or animal origin of bloodstains.

Present Investigation

In our investigations we have confined ourselves to the search for specific precipitins in the blood-serum of rheumatic children during the 'silent

[1] Received January 14, 1933.

period' following a throat infection, using as the antigen, or precipitinogen, filtrates of ground-up streptococci prepared by Dr. W. R. F. Collis. Two such antigens were used: one from a haemolytic streptococcus isolated from the acutely inflamed tonsils of a rheumatic child, who relapsed with a severe carditis; and the other from a typical *Streptococcus viridans*, obtained from a simple tonsillitis. The patient's serum in all cases was tested against the *Streptococcus haemolyticus* antigen, and in several also against that obtained from the *Streptococcus viridans* culture. The results were correlated with the type of streptococcus isolated from a throat culture, taken during the acute pharyngeal infection. At the same time careful watch was made for any signs of a rheumatic relapse, in order to prove whether or not such an occurrence bore any direct relation to the development of precipitins in the patient's serum. Concurrent with our investigations, Dr. W. W. Payne made a study of the blood sedimentation rate, the results of which will form the subject of a separate communication, although the figures will appear on the present charts and will therefore require a brief explanation.

Details of the laboratory technique adopted, which aimed at making a quantitative estimation of the precipitin content, will be found at the end of this article. The group of cases in which the investigations were carried out consists of seventeen rheumatic and four non-rheumatic children. In each the blood-serum was examined for precipitins during the acute naso-pharyngeal infection and afterwards approximately at weekly intervals. The results are graphically laid out in Table I, p. 264.

Precipitin Formation

A study of this table will reveal several interesting facts in regard to the formation of precipitins. In the first eight rheumatic cases, which showed no evidence of a rheumatic relapse following the acute throat infection, precipitin was found in the serum of one child only. She differed from the others in not having received aspirin or tolysin at the outset of the throat infection, and the possible bearing of this will be discussed later. The next four (9–12) serve as control cases; they are children who had never suffered from rheumatism but who contracted well observed acute throat infections. Beyond a period of rest in bed, they were left untreated. In one instance only was a faint precipitin reaction found. The remaining nine cases (13–21) are grouped together as either showing a tendency to relapse some weeks after the onset of the throat infection (Cases 13–18), or, as in Cases 19, 20, and 21, definitely doing so.

Tendency to a rheumatic relapse was recognized by a brief bout of pyrexia, one or two weeks' tachycardia, a drop in a previously increasing weight, the appearance of nodules in one case (Case 16), and in others a fresh rise in the blood sedimentation rate after it had satisfactorily subsided following the tonsillitis. These manifestations appeared at the end of a rather longer silent period than usual, but only in one instance (Case 18) was there reason

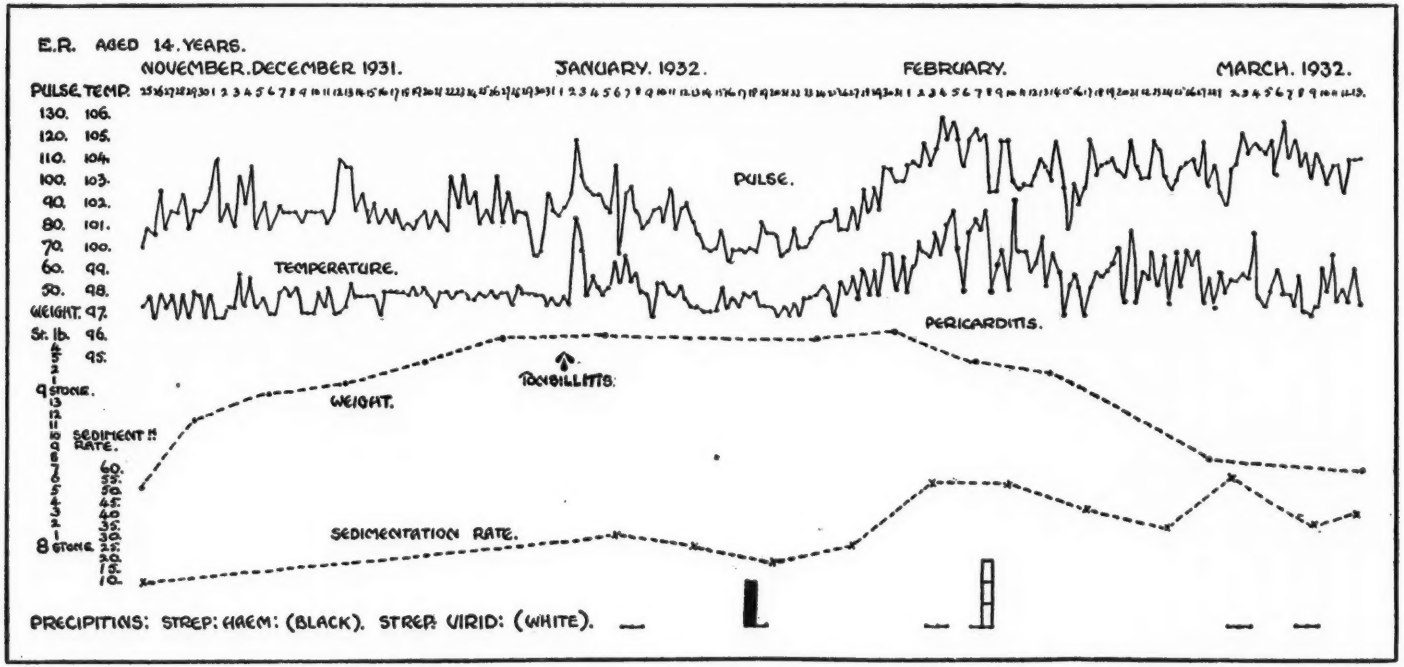

FIG. 1. Chart of Case 20 (see Table I) showing onset of acute tonsillitis, silent period, and rheumatic relapse with pericarditis. Note rise in sedimentation rate, drop in weight after steady gain, and appearance of precipitins to both streptococcal antigens in the patient's blood-serum. Throat culture during acute tonsillitis grew *Streptococcus haemolyticus*, but a predominance of *Streptococcus viridans*,

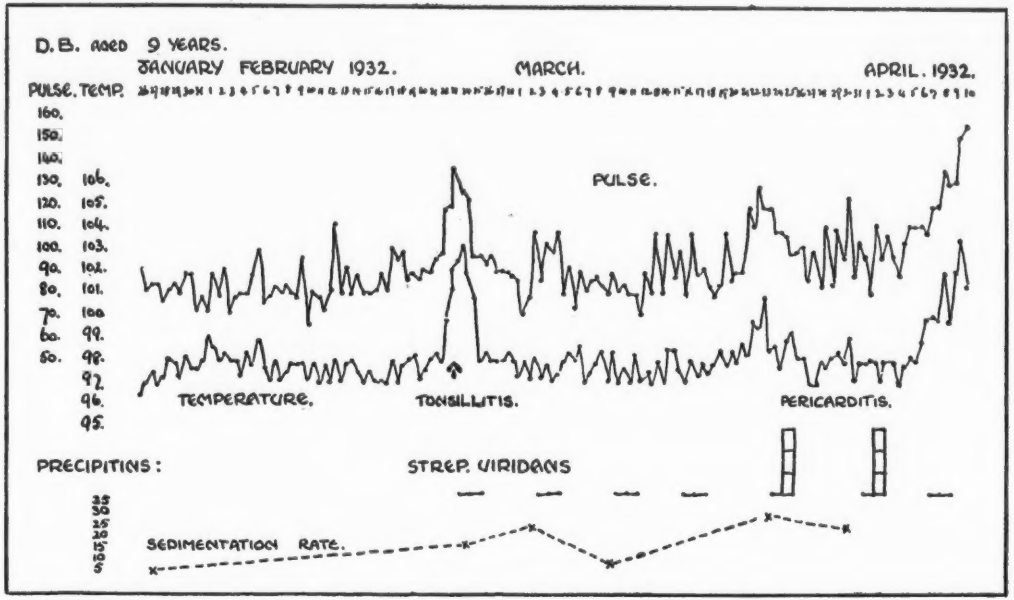

FIG. 2. Chart of Case 21 (see Table I) showing acute rheumatic relapse following tonsillitis with the usual silent period intervening. No haemolytic streptococci were cultured during the acute throat infection, but only *Streptococcus viridans*.

Precipitins to *Streptococcus viridans* were alone discovered.

to believe that the carditis had been reactivated, when some months later the original mitral regurgitation developed into mitral stenosis.

In the final three cases (19, 20, 21) rheumatic lapses were severe, and in the last two a fulminating pericarditis rapidly proved fatal.

It is in these two groups of cases—those with a tendency to relapse and those which definitely did so—that precipitin reactions made their appearance with any degree of regularity. They were demonstrated in seven out of the nine patients, being especially marked in the three last severe cases (see Figs. 1 and 2).

Specificity of Precipitin Formation

In collecting repeated samples of blood from our patients, we thought it wise to limit the amount taken on each occasion to 2 c.c., and the resulting small measure of serum only enabled us to perform quantitative tests against one or, at the most, two antigens. At the beginning of our investigations, therefore, we made use of the antigen prepared from a certain strain of haemolytic streptococcus. Tests against the second antigen derived from a *Streptococcus viridans* were also undertaken in a few. In the last two fatal cases (20 and 21) this proved of sufficient interest to warrant more detailed comment. The throat culture of Case 20 grew both types of streptococci, although the viridans strain was in predominance. Precipitins in the patient's serum were found against both antigens, though their presence seemed not to coincide. In Case 21 *Streptococcus viridans* was alone responsible for the tonsillitis, and precipitins appeared only to the *Streptococcus viridans* antigen; there was no reaction with the haemolytic streptococcus antigen. The number of cases in which the patient's serum was tested against both antigens were too few to draw any definite conclusions, and we can only point to the interesting correlation which existed between the organism responsible for the throat infection and the type of precipitin which made its appearance. At the same time Cases 6 and 10 show that the specificity of the reaction is not always so exact, since here the throat cultures showed no haemolytic streptococci to be present, and yet later precipitins to this organism appeared. Further researches obviously will be required, especially into this point of specificity, which will also have to include other antigens entirely unconnected with the whole group of streptococci.

Time Relationship and Strength of the Precipitin Reaction

In no case were precipitins discovered at the time of the acute throat infection. In our series the earliest appearance noted was at the tenth day, but in one case it was delayed until the thirtieth day after the onset of the tonsillitis. With weekly blood examinations these figures can only be approximate, but it did not seem justifiable to bleed our patients more frequently

in order to ascertain the exact date of precipitin formation. As already noted, in all but two cases precipitin reactions were associated with rheumatic relapses, mild or severe. It was noticed that precipitin appeared in the blood at the time of the relapse, or more usually about one week prior to the renewed clinical manifestations (see Figs. 1 and 2). Once the rheumatic relapse was well under way, the precipitins disappeared again; their presence in the patient's serum was short-lived, and already in one or two weeks they were gone.

The Effect of Aspirin

One of us (1) has expressed the view that a three or four weeks' course of aspirin from the onset of the tonsillitis will prevent severe cardiac rheumatic relapses occurring in many cases. This treatment was not regarded as infallible, and Case 21 is a good example of such failure.

Derick, Hitchcock, and Swift (5) declare that an adequate dosage of aspirin, or neocinchophen (tolysin), given to patients for a period of ten to fourteen days following an injection of horse serum, usually prevented the formation of precipitin. Although this did not hold true in our series in regard to streptococcal precipitins, aspirin and tolysin appeared to have some effect. It is significant that the one child who gave a marked precipitin reaction, and yet failed to show signs of rheumatic relapse, had not been treated with aspirin (Case 6). The same can be said of one of the controls (Case 10), although here the precipitin reaction was very faint. In addition it was found that when, despite aspirin, precipitins were formed, their appearance was distinctly delayed, compared with those cases in which this treatment had not been adopted.

Sedimentation Rate

Reports have already appeared by Payne (6), Gray Hill and Bach (7) (8), on the effect of active rheumatism on the erythrocyte sedimentation rate. We fully agree with their conclusions, which stated that the sedimentation rate (S. R.) was raised during the active rheumatic phase and dropped to normal as it became quiescent. All are agreed that the S. R. is a non-specific reaction and that any active infection will raise it.

In Table I we have added Payne's figures in this series. Those in the third column (under previous history), taken before the onset of tonsillitis, are for the most part normal, which agrees with the clinical evidence of a quiescent phase of their rheumatism.[2]

The bulk of figures will be found in the sixth column. In the first nine cases it is quite evident that tonsillitis alone is sufficient to raise the sedi-

[2] The initial high figure of 20 in Case 3 would be accounted for by the presence of congenital syphilis.

mentation rate for a considerable time, but that eventually it can be traced back to a normal figure in most cases (seventh column under rheumatic relapse). On the other hand, in Cases 13 to 21, after an attempt to drop towards normal, a fresh rise is noted corresponding to the reactivation of the rheumatism.

Discussion

The most interesting outcome of this investigation, to our minds, is the fact that precipitins are formed at all in the blood of patients who have undergone such mild and fleeting throat infection. This gives their special association with rheumatic relapses, subsequent to pharyngitis or tonsillitis, an added significance. The interval that elapses before their advent between the second and fourth week is to be expected, and follows closely the course of antibody formation in general during acute infections.

Jorensen (9), for example, worked out the time-interval before agglutinins appeared in the blood-serum of patients suffering from enteric fever. He found a somewhat sudden rise, reaching its maximum towards the end of the third week, and declining rapidly long before the disease had run its course. His charts are very reminiscent of ours, but with one great difference; whereas his time intervals count from the actual onset of the typhoid, ours date from the beginning of the pre-rheumatic throat infection. In this way the peak of streptococcal precipitin formation coincides roughly with the commencement of the rheumatic relapse after the silent period.

The first researches into precipitin formation were in connexion with injections of horse serum in man. Most of the earlier investigators are agreed that precipitins appear on the eighth to sixteenth day, and after serum sickness has begun—never before (10–15). Nevertheless, most of them pointed to a probable relationship between serum sickness and precipitin formation, but would not testify to Pirquet and Schick's (10) original contention that the serum reaction was caused through the clash of antigen and antibody. Hamburger and Moro (11) found precipitins in the blood of rabbits about eight days after a single injection of horse serum. Dean (16), on the other hand, with a newer technique, found difficulty in demonstrating any precipitin at all with a single dose. In the one instance in which he succeeded, it made its appearance in any quantity on the *twenty-first* day. Lloyd Jones and Fleisher (17) claim to have demonstrated serum disease in rabbits by an erythema and localized oedema confined to the ears. They find no evidence to associate directly the occurrence of this type of serum reaction with the production or appearance of precipitins in the blood. The question remains, however, whether the phenomenon in rabbits can in any way be compared to serum sickness in man. At the moment it seems that our knowledge of the exact part played by immunology in the production of serum sickness is incomplete. To state

anything definite in this connexion as regards acute rheumatism would thus certainly be premature; neverthless, the resemblance as regards precipitin formation in serum disease and acute rheumatism is too close to pass unnoticed. The demonstration of streptococcal precipitins, principally in association with acute rheumatic relapses following streptococcal throat infections, appears to us of major importance, and is strong evidence in favour of Poynton and Paine's original theory of the bacteriology of rheumatism. Their delay in appearing also explains, to a certain degree, the existence of a silent period.

As already noted, precipitins to the haemolytic streptococcus were not found exclusively. From this one might reasonably argue that in rheumatism the haemolytic streptococcus is not alone responsible, *Streptococcus viridans*, for instance, being in some cases an equally potent bacteriological factor. Eventually, a common streptococcal nucleo-protein, or some other integral part of the organism, may prove to be the essential cause of the disease. Hence it would seem wise to contemplate a broad bacteriological horizon, and keep in mind the *genus Streptococcus*, rather than narrow the field to one particular strain.

Laboratory technique. The technique adopted for the precipitin test was necessarily modified so as to make the best use of small amounts of serum and yet attempt to obtain a quantitative result. The antigen used was provided by Dr. Collis, and its preparation has been described in detail by him (3). It consists of a filtered saline emulsion of ground streptococci. Standard dilutions of the patients' sera to be tested were made. In the early part of the work a 1/10 dilution was used, but later it was found that a 1/5 dilution gave better results. One c.c. of this serum was put up against 1 c.c. of falling dilutions of the antigen, 1/5, 1/10, 1/20, and 1/40 being the dilutions most commonly used. Dilutions were at first made both with normal saline and with 0·2 per cent. NaCl, but as no differences were noted, normal saline only was used in the later tests. It was presumed that if precipitins were present in the samples of blood, reactions might be expected from the whole organism concerned. Further research is now in progress to determine which fraction of the micro-organism is responsible for the reaction, and it seems likely that the separated nucleo-protein will give better results than those achieved with the whole organism.

Results. These were never readable in one hour, but were usually definite after twelve hours, incubated in a 37° C. water bath. Occasionally they were more easily demonstrated after a further twelve hours in an ice-chest. A control tube of serum and saline was always used, and occasionally showed turbidity after incubation. When this occurred the serum was discarded as unsuitable for the test. The positive reactions were never very heavy precipitates. A flocculent deposit with a clouding of the supernatant fluid was taken to denote a strong positive reaction, whilst a mere clouding with or without a very slight deposit in one or two tubes was read as a weak positive reaction, provided always that the control tube remained clear. Reactions were more frequently observed in the tubes containing the more concentrated antigen and never showed a 'zone phenomenon'.

The results were quite clear cut and easily read by the naked eye, but they were always confirmed with a hand lens.

Conclusions

1. Streptococcal precipitins can be demonstrated in the blood of rheumatic patients following acute streptococcal throat infections.

2. Their formation is delayed until the second to fourth week from the onset of the nasopharyngeal infection (the end of the silent period), and their appearance in most cases foreshadows a tendency to a relapse of acute rheumatism.

3. The precipitin corresponds to the type of *Streptococcus* responsible for the throat infection, but a certain amount of cross precipitin formation may occur.

4. The formation of precipitin is regarded as one of the manifold reactions which take place in the patient's defence mechanism during the silent period. There is thus time for prophylactic measures if the throat infection has not passed unnoticed. Concentrated aspirin therapy during this period undoubtedly prevents serious relapses in many cases. It is not infallible, and further researches are urgently required to discover some other method which is still more reliable.

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On going to press we have just received from Dr. Coburn in America the results he and Dr. Pauli obtained whilst working along similar lines to ours. It is of great interest to find that in regard to precipitin formation their conclusions are in close agreement with ours. (See *Journ. Exper. Med.*, N. York, 1932, lvi. 609.)

TABLE I

S.R. = Sedimentation rate of the blood. A = Aspirin begun at onset of throat infection. T = Tolysin begun at onset of throat infection.
Ⓐ = Aspirin begun one week after onset of throat infection. Pptn. H. = Precipitin with haemolytic streptococcus antigen.
Pptn. V. = Precipitin with viridans streptococcus antigen.

Case.		Previous history.	Heart lesion.	Type of throat infection.	Precipitin reaction and sedimentation rate. Number of days after onset of throat infection.	Rheumatic relapse.	Nature of relapse.
1	A	Rheum. fever	Nil	Strep. haem.	Pptn. H. Negative on the 6th, 13th, and 20th days	Nil	—
		S.R. 12			S.R. 17 on the 5th and 17 on the 12th day	S.R. 10	
2	T	Indefinite	Mitral regurg.	Strep. haem.	Pptn. H. Negative on the 3rd, 10th, and 17th days	Nil	—
		S.R. 14, 23			S.R. 21 on the 2nd, 44 on the 9th, 64 on the 16th, and 47 on the 23rd day 31 on 31st day	S.R. 13	
3	A	Rheum. fever W.R. positive	Mitral stenosis	Strep. haem.	Pptn. H. Negative on the 3rd, 21st, and 40th days	Nil	—
		S.R. 20			S.R. 40 on the 9th, 66 on the 16th, 45 on 36th day	S.R. 20	
4	T	Rheum. fever	Mitral regurg.	—	Pptn. H. Negative on the 8th and 15th days	Nil	—
		S.R. 7			S.R. 19 on the 7th, 18 on the 14th, and 12 on the 21st day	S.R. 8	
5	A	Chorea, nodules	Mitral regurg.	Strep. haem.	Pptn. H. } Negative on the 4th and 25th „ V. } days	Nil	—
		S.R. 14		Strep. viridans	S.R. 20 on the 11th day	S.R. 18	
6	—	Subacute rheum.	Nil	Strep. non-haem.	Pptn. H. Negative on the 5th day, *positive* on the 16th and 32nd day, negative on 36th day	Nil	—
		S.R. 5		Ungrouped	S.R. 4 on the 18th day	S.R. 5	
7	A	Subacute rheum.	Mitral regurg.	Strep. haem.	Pptn. H. Negative on the 2nd and 23rd day	Nil	—
		S.R. 3		Strep. viridans	S.R. 13 on 9th day	S.R. 5	
8	A	Subacute rheum.	Myo-carditis	—	Pptn. H. Negative on 11th, 25th, and 40th days Pptn. V. Negative on 25th and 40th days	Nil	—
		S.R. 7			S.R. 50 on the 5th, 43 on 11th, 33 on 18th, 17 on 32nd, and 20	S.R. 6	

					Pptn. V.	Negative on 25th and 40th days		
		S.R. 7			S.R.	50 on the 5th, 43 on 11th, 33 on 18th, 17 on 32nd, and 20 on 37th day	S.R. 6	
9	A	Non-rheum. S.R. 9	Nil	—	Pptn. H. S.R.	Negative on 26th day 35 on 18th day	Nil S.R. 53, 8	Pyrexia. Acute otitis 22 days after throat infection
10	—	Asthma	Nil	Strep. viridans Staph. aureus.	Pptn. H. ,, V.	Negative on 2nd, 8th, and 22nd days. *Positive* on 15th day Negative on 2nd, 8th, and 22nd days	Nil	—
11	—	Nil	Nil	Strep. haem. Strep. viridans	Pptn. H. ,, V.	Negative on 2nd, 7th, 15th, and 22nd days Negative on 2nd and 7th days	Nil	—
12	—	Congenital syphilis	Nil	Strep. viridans	Pptn. H. ,, V.	Negative on 1st, 7th, 14th, and 21st days Negative on 1st, 7th, 14th, and 21st days	Nil	—
13	A	Rheum. fever S.R. 9	Mitral stenosis	Strep. haem.	Pptn. H. S.R.	Negative on the 6th, 13th, and 44th days. *Positive* on 24th day 24 on 5th, 24 on 12th, 17 on 19th, 14 on 26th, and 35 on 40th day	Tendency S.R. 5, 23, 11	Transient tachycardia 4th week. Drop in wt. Fresh rise in S.R. 4th week
14	A	Chorea. Subacute rheum. S.R. 9	Mitral regurg.	Strep. haem.	Pptn. H. S.R.	Negative on 6th, 13th, and 39th days. *Positive* on 23rd day 10 on 5th, 16 on 18th, 17 on 32nd, and 41 on 37th day	Tendency S.R. 18, 14, 6	Transient pyrexia and tachycardia, 4th and 5th week. Fresh rise in S.R.
15	—	Rheum. fever S.R. 16	Nil	Strep. haem.	Pptn. H. S.R.	Negative on 3rd, 9th, 24th, and 31st days. *Positive* on 14th day 31 on 9th, 13 on 17th, 20 on 24th, 25 on 31st, and 23 on 36th day	Tendency S.R. 17	Transient pyrexia end of 4th week. Fresh rise in S.R. Drop in wt.
16	A	Rheum. fever. Chorea S.R. 11	Mitral stenosis	Strep. haem.	Pptn. H. S.R.	Negative on 14th, 22nd, 29th and 36th days 32 on 8th, 52 on 14th, 59 on 22nd, 45 on 29th, 42 on 36th day	Tendency S.R. 17, 15	Recurrence nodules only 9th week. No further carditis

TABLE I (*continued*)

Case.		Previous history.	Heart lesion.	Type of throat infection.	Precipitin reaction and sedimentation rate. Number of days after onset of throat infection.	Rheumatic relapse.	Nature of relapse.
17	Ⓐ	Subacute rheum.	Mitral stenosis	Strep. haem.	Pptn. H. Negative on 21st, 27th, and 34th days. *Positive* on 10th day	Tendency	Transient pyrexia. Drop in wt. Persistent raised S.R.
		S.R. 7		Strep. viridans	S.R. 33 on 5th, 33 on 13th, 21 on 19th, 18 on 27th, 44 on 34th day	S.R. 24, 18	
18	A	Rheum. fever	Mitral regurg.	Strep. haem.	Pptn. H. Negative on 2nd, 10th, and 17th days	Mild, slow	Tachycardia 5th week. Further development endocarditis (mitral stenosis)
		S.R. 14			S.R. 28 on 2nd, 54 on 9th, 43 on 16th, 32 on 23rd, 20 on 30th, and 16 on 36th day	S.R. 18, 12, 10	
19	A	Rheum. fever	Mitral stenosis	Strep. haem.	Pptn. H. Negative on 4th, 11th and 49th days. *Positive* on 18th and 29th days	Well marked	Pyrexia followed by nodules and chorea
		S.R. 7			S.R. 34 on 3rd, 23 on 10th, 23 on 17th, 43 on 24th, 33 on 31st, and 18 on 37th day	S.R. 35, 13, 11	
20	—	Rheum. fever. Chorea	Mitral stenosis	Strep. viridans	Pptn. H. Negative on 6th, 33rd, 37th, 61st, and 68th days. *Positive* on 17th day	Severe	Pyrexia. Tachycardia 4th week. Pericarditis. Nodules. Death
		S.R. 10		Strep. haem.	,, V. Negative on 61st and 68th days. *Positive* on 37th day	S.R. 40, 53	
					S.R. 31 on 5th, 25 on 12th, 18 on 19th, 26 on 26th, 54 on 33rd, 54 on 40th, 57 on 61st, and 36 on 68th day		
21	A	Rheum. fever	Mitral regurg.	Strep. viridans	Pptn. H. Negative on 3rd, 10th, 17th, 24th, 31st, 39th, and 45th days	Severe	Pyrexia. Tachycardia. Rheumatic rash. Pericarditis. Nodules. Death
		S.R. 5			,, V. Negative on 3rd, 10th, 17th, 24th and 45th days. *Positive* on 31st and 39th days		
					S.R. 16 on 3rd, 25 on 10th, 9 on 17th, 30 on 31st, 25 on 39th day		

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DIABETIC LIPAEMIA[1]

THE ROLE OF THE FATS IN DIABETES MELLITUS, WITH A DESCRIPTION OF THE HAEMOLIPOKRIT METHOD FOR THE ESTIMATION OF FAT IN THE BLOOD-SERUM.

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Introduction

It has been known for a long time that a disturbance of fat metabolism is associated with diabetes mellitus. Both the fatty appearance of the liver *post mortem*, and the milky condition of the serum of certain diabetic cases have attracted attention. This milky, or chylous, condition of the serum was termed 'lipaemia', though now, in the days of more exact chemical methods, the term is used to denote any increase of fat in the blood above the normal, whether the serum is opalescent or not.

Although much work has been done on the physiology and the biochemistry of the fats, little is known of the relationship that fat metabolism bears to the metabolism of carbohydrates, and therefore, any light on this subject will bear not only on the study of physiology but also on the study of such clinical conditions as diabetes.

Liebig, referring to the fat produced by a milch-cow in its milk, in excess of the fat of its food, was the first to suggest the synthesis of fat within the animal body, and in spite of some early experimental results to the contrary, there is no lack of biological evidence that the carbohydrates are concerned in this process. The chemical procedure most probably involved is that known as 'aldol condensation'.

The utilization of fat has been widely studied. Apart from that fraction so intimately connected with cellular structure that it cannot be mobilized during life—the 'élément constant' of French scientists—fat is a potent source of energy and is ultimately oxidized to carbon dioxide and water. The theory that fat, in plants, is transformed into carbohydrate is supported by the evidence of several workers, but the chemical processes involved are not clear. This may also occur within the animal body, as is suggested by the very low respiratory quotient of hibernating animals (Pembrey, 1903), but excepting the glycerol component there is no indication as to how this takes place.

The chemistry of fat oxidation in the animal body is not yet fully elucidated, but whether this proceeds by a simple β-oxidation, or by the formation of intermediate keto- or unsaturated acids, the long chain fatty acids

[1] Received January 24, 1933.

lose two carbon groups at a time, so forming an acid of smaller molecular weight. Oxidation continues until the four carbon-atom acids are formed, but ceases at this stage unless glucose is also oxidized. These acids, representing the stage at which fat catabolism is held up, are aceto-acetic acid ($CH_3CO\ CH_2COOH$) and β-hydroxybutyric acid ($CH_3CHOH\ CH_2COOH$), and appear in the urine and the blood of patients suffering from a severe carbohydrate starvation, whether this is absolute, as in fasting, or relative, as in the diminished carbohydrate combustion of diabetes. In discussing the figures presented below, the occurrence of acetonuria is considered as being indicative of severe disturbance of carbohydrate metabolism, rather than of fat metabolism primarily.

There are here, then, three links between fat and carbohydrate metabolism: (1) the certain conversion of carbohydrate into fat, (2) the formation of carbohydrate from fat, most probable in plants and possible in animals, and (3) the dependency of the final stages of fat oxidation on the simultaneous combustion of glucose.

That fat can be, and is, utilized directly by the diabetic has been sufficiently demonstrated. Lafon (1913) was the first to show that fats were directly utilized by the muscles in activity, and Patterson (1927) discovered an increase of the blood-fats in humans during muscular exercise. Stewart, Gaddie, and Dunlop (1931) found this lipaemia to develop after a certain amount of work had been done, and the respiratory quotient fell. From an analysis of the oxygen consumption and nitrogen excretion they deduced that additional fat and not protein was being used. The iodine value of the fats responsible for this lipaemia, which were mostly neutral fats, never rose in amount, and from this observation they came to the same conclusion as Imrie (1915) that the source of the added fats was the adipose connective tissue. In diabetics with a high-resting blood-fat the amount of blood-fat first fell and then rose when work was done, and though performing work at a lower respiratory quotient, diabetics showed no loss of efficiency and no oxygen waste, and there was, therefore, no conversion of fat into carbohydrate. In this connexion Lusk (1928) summarizes the arguments against the possibility of fat being converted into carbohydrate and expresses the definite opinion that this does not occur in diabetes. Lusk adds that though the administration of glycerol may increase the glucose excretion, the glycerol originating from fat in diabetics is oxidized with the fatty acids simultaneously liberated.

The types of fat present in human blood are, chiefly, neutral fats (triglycerides), lecithin, cholesterol, and cholesterol esters. The proportion of these separate constituents varies considerably, but we may summarize by saying that in the normal fasting animal triglycerides are not present to any great extent in the blood, that lecithin is present in greater amount in the corpuscles than in the plasma, and that cholesterol, which is present in plasma and corpuscles in about equal parts, is combined, in the plasma, to the extent of some 50 per cent. with fatty acids, forming cholesterol esters.

Increase of fat in the blood occurs after the ingestion of fat from the intestine, in pregnancy, in phosphorus and phloridzin poisoning, after severe haemorrhage, and in diabetes, and may be classed as exogenous or endogenous lipaemia.

The excess of fat in the blood in the exogenous type has its origin directly in the fat absorbed from the intestine. There is an alimentary hyperlipaemia after food comparable to the alimentary hyperglycaemia, but differing from the latter in being prolonged over a longer period. The rise of fatty acids occurs two to six hours after food, and of cholesterol four to seven hours after food (Bloor, 1915). The existence of an endogenous lipaemia has often been ignored, but that it may arise is proved by evidence mainly derived from animal experiments. Horiuchi (1920) obtained a lipaemia in rabbits by repeated bleedings, even though the animals had received a diet from which fat had been excluded. There appears, furthermore, to be a qualitative difference in the fats found in the blood in exogenous and endogenous lipaemias. In the former—the alimentary type—the most notable quantitative increase is of lecithin, and particularly of that in the corpuscles. The increase of cholesterol is small and irregular, probably being dependent on the amount of cholesterol in food or bile that is available in the intestine. In the endogenous lipaemia there is, characteristically, an increase of the total fatty acids and an absence of increase of lecithin, and in the case of diabetes the cholesterol appears to rise in a manner parallel to the fatty acids (Bloor, 1916). The increase of fat in pathological lipaemias is almost entirely confined to the plasma.

Although many workers have investigated the blood-fats in diabetes, their work has not been followed up, and many points still require elucidation, largely owing to the difficult or laborious technique necessary for blood-fat estimation. And for these reasons the routine investigation of blood-fats has never had the consideration that the time-honoured and simpler blood-sugar estimation has received.

Recently, however, a simple method for the volumetric estimation of fat in small quantities of serum has been found. This is the 'Haemolipokrit' which was suggested and described by Dr. Rückert of Marburg and has been used here in a series of investigations on diabetic patients.

Experimental Technique

The technique used was that described in Rückert's original article (1931), with such modifications as were found useful, and will be described in detail. All the apparatus was supplied by Messrs. Emil Busch of London.

The haemolipokrit. The method is one for the volumetric determination of the total fat content of serum, and is identical in principle with the Gerber method for estimating fat in milk.

Hydrolysis of the proteins, causing their change from a colloidal state to a state of molecular dispersion, is effected by concentrated sulphuric acid. This allows the liberation of the fats, which, by standing or centrifugalizing,

separate out and can be measured volumetrically in a vessel specially constructed with a graduated scale.

Reagents. An acid concentration is required which is sufficiently high both to hydrolyse the proteins and, by virtue of its specific gravity, to permit the separation of fat on centrifugalizing, but which must not be so high as to alter the serum fats. The optimum concentration Rückert found to be 70 per cent. of H_2SO_4 (S. G. 1616), to be used in a ratio of 4 parts of acid to 1 of serum. A small quantity of amyl alcohol (1 part to 12·5 of acid) is also used, as in the Gerber process, to aid the separation of the fat.

In order to facilitate the reading, the acid is coloured by 0·08 per cent. of methylene blue, which does not pass into the fat, and the amyl alcohol is used as a carrier for a fat soluble yellow stain—aniline yellow. The reagents are thus:

Solution I.	Aniline yellow	0·075 c.c.
	Amyl alcohol	50·0 c.c.
Solution II.	Methyleum coer. med. . . .	0·12
	70 per cent. sulphuric acid . . .	150·0 c.c.

Three drops of Solution I are mixed with 25 drops of Solution II immediately before use. The solutions are obtainable from Messrs. Emil Busch in special drop bottles.

The Haemolipokrit Pipette (Fig. 1)

FIG. 1.

This consists of a small lower ampulla into which serum may be sucked (A). This is connected by a capillary tube to a larger mixing chamber (B), into which the serum and the acid-alcohol mixture may be drawn and mixed by means of a small glass bead. Leading out of this ampulla is a graduated capillary (C) in which the fat collects during centrifugalizing. The scale and the ampullae have no specific size, but bear a constant relation to one another. On the average, the absolute capacity of the serum chamber amounts to about 0·15 c.c. The serum chamber, mixing chamber, and whole scale bear the proportions of 25 : 125 : and 1.

The mixing chamber after filling thus contains the proportion of 1 part of serum to 4 of acid-alcohol mixture. Each graduation of the capillary represents a certain percentage of the capacity of the serum ampulla. The whole scale reads 4·00 c.c. per cent. and each smallest division corresponds to 0·04 c.c. per cent.

Method. Special U-shaped capillary tubes are provided for receiving the blood from cutaneous puncture, but it is easier to collect the samples in small centrifuge tubes, after venipuncture with a clean dry needle. Only 1 to 2 c.c. of blood are required. After clotting, the blood is centrifugalized, as the estimation is made on serum. Slight haemolysis does not

appear to affect the results, but corpuscular bodies must be rigorously excluded, as they form clumps during hydrolysis with the acid and are liable to block the pipette. For this reason it is better to use serum expressed from clot and centrifugalized than plasma obtained by the centrifugalizing of citrated or oxalated blood, though the figure so reached varies only in a negligible degree from that obtained when using plasma.

The serum ampoule is filled with serum, the exuding drop wiped off, and the pipette filled with the prepared acid-alcohol mixture up to about the 50 mark on the scale. The pipette is then held horizontally between the palms of the hands and briskly rotated to ensure a thorough mixing. The serum remaining in the capillary scale is repeatedly blown back and sucked up until well mixed. This must be done with care, in order not to lose any fluid or introduce air-bubbles. Following this, the pipette is dipped into the acid again and the fluid sucked up to the 100 mark. After clamping the pipette in the metal holder (Fig. 2), the apparatus must be well shaken.

FIG. 2.

Rückert claims that the amount of neutral-fat and cholesterol can be read off if centrifugalizing takes place within thirty minutes, and the total fat after a second centrifugalizing eighteen to twenty-four hours later. This first reading, in our hands, gave results which are obviously unreliable and it was therefore ignored.

The pipettes in their frames are placed in a 37° C. incubator for twenty-one to twenty-four hours and are then centrifugalized.

The height of the fat column, stained yellow, in the capillary tube is now read off at room temperature. If the lower meniscus is not clearly defined, that part of the tube in which it lies should be gently warmed over a small bunsen flame, and allowed to cool. Should the pipette be imperfectly filled and none of the fat lie over the scale, then the Lipokrit should be placed erect in a water-bath at 45° C. until expansion of the fluid ceases, then removed and the fat column measured as it retreats on cooling.

Confirmatory Experiments

As the method was a new one, it was considered necessary to undertake confirmatory experiments with a view to estimating what relation the volumetric Lipokrit results bear to results obtained by more elaborate gravimetric methods.

Three different sera were used. Four Lipokrit estimations were made in each case and the fat content of each serum was determined by the Shimidzu combined alcohol extract technique (Shimidzu, 1910). More than 25 c.c. of serum are required for this latter method. The result, expressed in grammes per cent., is the weight of fatty acids together with cholesterol obtainable from 100 c.c. of serum, and is compared with the result determined, volumetrically, by the Lipokrit which measures the neutral fats, fatty acids of lecithin, and cholesterol.

Experiment I.

Serum of sheep's blood.
Gravimetric result: 0·167 grm. per cent.
Lipokrit results: (i) 0·20, (ii) 0·20, (iii) 0·20, (iv) 0·20 c.c. per cent.
Average: 0·20 c.c. per cent.

$$\text{Ratio: } \frac{\text{Lipokrit c.c. per cent.}}{\text{Gravimetric grm. per cent.}} = 1{\cdot}198.$$

Experiment II.

Pooled Wassermann sera (after six to ten weeks).
Gravimetric result: 0·6013 grm. per cent.
Lipokrit results: (i) 0·70, (ii) 0·70, (iii) 0·68, (iv) 0·72 c.c. per cent.
Average: 0·70 c.c. per cent.

$$\text{Ratio: } \frac{\text{Lipokrit c.c. per cent.}}{\text{Gravimetric grm. per cent.}} = 1{\cdot}160.$$

Experiment III.

Pooled Wassermann sera (after three to five weeks).
Gravimetric result: 0·530 grm. per cent.
Lipokrit results: (i) 0·66, (ii) 0·68, (iii) 0·70, (iv) 0·68 c.c. per cent.
Average: 0·68 c.c. per cent.

$$\text{Ratio: } \frac{\text{Lipokrit c.c. per cent.}}{\text{Gravimetric grm. per cent.}} = 1{\cdot}280.$$

The results have been expressed as ratios of c.c. per cent. to grm. per cent., these three figures being 1·198, 1·160, and 1·280 : Mean = 1·213. There is, however, no indication that the gravimetric result should bear any close relation to the volumetric in a number of specimens in which the proportion of the constituents, e.g. cholesterol (S. G. 1·07) and oleic acid (S. G. 0·89) may vary. The real interest of these results lies in the uniformity of the Lipokrit readings in each case, the only variation from the mean being less than 3 per cent.

The Lipokrit method was, therefore, considered convenient and sufficiently accurate for the clinical determination of serum-fats.

Investigation of Clinical Cases

Serum-fat estimations were made on fifty-five sera from fifty-three non-diabetic cases, and on 103 sera from fifty-two diabetic cases.

In most cases the serum used for the controls was that sent over to the laboratories for Wassermann test. The estimations were carried out from six to forty-eight hours after the drawing of the blood. Delay in examination seemed in no way to influence the result, provided that a fair sample be taken for the estimation and not just 'cream'.

The majority of the diabetic cases chosen for this investigation were those attending the Out-Patients' Clinic at the David Lewis Northern Hospital, Liverpool, and all except two had received either dietetic or insulin treatment. These cases are, therefore, representative only of a mild type of diabetes, and of such as have responded well to treatment.

Average serum-fat content in diabetes.

	No. of cases.	*Mean serum-fats c.c. %.*
Non-diabetic cases.		
Male	38	0·566
Female	17	0·588
Totals	55	0·571
Diabetic cases.		
Male	10	0·948
Female	93	0·805
Totals	103	0·818

Average blood-fats from Joslin, Bloor, and Gray (1917).

Normal	19	0·59 grm. %.
Diabetics	124	
Mild	—	0·83 ,,
Moderate	—	0·91 ,,
Severe	—	1·41 ,,

The highest individual serum-fat reading was 1·48 c.c. per cent. in a diabetic whose blood-sugar was only 98 mg. per 100 c.c., and who, although receiving 15 units of insulin daily, showed glycosuria and acetonuria.

The lowest serum-fat encountered was 0·26 c.c. per cent. in a non-diabetic case suffering from hyperthyroidism.

The average diabetic serum-fat exceeds that of the non-diabetic cases by 0·247 c.c. per cent., representing an increase of 42·2 per cent. of the non-diabetic average.

Period of starvation. The figures obtained by Bloor (1915) show that the increase in plasma-fats occurs in the case of fatty acids from two to six hours after food, and in the case of cholesterol from four to seven hours after. These figures are confirmed by Knudson (1917) in dogs. The majority of our blood samples were collected after three hours' starvation. The increase in serum-fats after a normal meal is probably so small as compared with the serum-fat increase in a pathological lipaemia as to be of no consequence in these results.

Body-weight. No relation exists between the body-weight of the individual and the concentration of fat in the serum, as is shown by reviewing the weights of those persons in whom the serum-fats are high (1·00 per cent. and over). These cases show a considerable divergence of weights:

Serum-fats. c.c. per cent.	Weight of body. lb.	Serum-fats. c.c. per cent.	Weight of body. lb.
1·00	199	1·14	105
1·04	162	1·16	118
1·06	87	1·32	154
1·12	140	1·32	84
		1·48	118

Diet. All but three cases have been dieted. Particular attention has not been paid to the antiketogenic formula $F = 2C + P/2$, and this ratio was often greatly exceeded. Since these patients were out-patients the diet was adjusted with a view to keeping the urine free from sugar and acetone, without having recourse to insulin. In theory, it would have been better to have made the fat estimations on blood taken after a twenty-four hours' fast, but in accommodating oneself to hospital routine this was impossible. The blood was collected for the fat determination at the same time as was that for the blood-sugar estimation and the patients were instructed to present themselves three hours after a meal. The work of Marsh and Waller (1923) is important in this connexion. They made a series of blood-fat estimations on diabetics treated by a high fat diet (fat up to 4 grm., per kilo. body-weight, per diem). In all cases there was a decrease of the blood-fat corresponding to the clinical improvement of the patient, while there was an increase of fat in the diet. The majority of our cases were on a moderately high fat diet. The influence of diet fat on serum-fat in diabetes is, in our opinion, negligible.

Insulin. The effect of insulin on the serum-fats is difficult to assess from a study of this series of cases, for the majority had been under treatment for some time, and only those patients whose disease could not be controlled by diet alone received insulin. In these cases the dose of insulin was the minimal required to keep the urine sugar-free. A marked fall in the serum-fats after insulin is, however, observed in one patient.

Case 8. S. J., male, aged 15 years. Admitted to hospital in a drowsy state. Condition had not previously been diagnosed or treated.

Date.	Insulin units per diem.	Diet.	Blood-sugar mg. %	Glycosuria.	Acetonuria.	Serum-fat. c.c. %
18.2.32	Nil	Nil	333	pres.	pres.	1·20
22.2.32	60	CHO restricted	50	Nil	Nil	0·68
24.2.32	30	CHO restricted	200	Nil	Nil	0·80

With smaller doses of insulin, its effect on the blood-fats is less easy to demonstrate, which finding is in agreement with Wilder and his co-workers (1922). Joslin (1923, a) records a few cases showing a decrease of blood-fats which occurred after some weeks of insulin treatment, and he quotes a case of Bock, Field, and Adair in which the blood-fat fell from 10·5 to 6·27 per cent. four hours after insulin and subsequently to 4·37 per cent. in thirty-six hours. Campbell (Campbell and Macleod, 1924) states that the blood-fats tend to fall rather slowly during insulin treatment. The disappearance of the lipaemia he considers to be more rapid in those cases where no fat is being fed to the patient and in which acidosis is rapidly abolished.

The action of insulin in diminishing the degree of lipaemia has been more satisfactorily demonstrated in experimental diabetes, but it is probable that

such a diminution would be observed in every human case if the dosage of the drug were sufficiently large.

Glycosuria. The urine was collected at the time of taking the blood samples in ninety-seven of the diabetic cases examined. Forty-seven specimens gave a positive reaction with Fehling's solutions, while fifty were free from sugar. An increased average serum-fat is noticed in those cases with glycosuria.

	With glycosuria.			Without glycosuria.		
	Male.	Female.	Total.	Male.	Female.	Total.
No of cases	5	42	47	5	45	50
Serum-fats, c.c. per cent.	1·070	0·843	0·868	0·820	0·759	0·766

Acetonuria. Of the same ninety-seven cases, eleven gave a positive ferric-chloride test on the urine. All these eleven cases also had glycosuria. A more striking increase of the serum-fats is observed in those with acetonuria.

	With acetonuria.			Without acetonuria.		
	Male.	Female.	Total.	Male.	Female.	Total.
No. of cases	4	7	11	6	80	86
Serum-fats, c.c. per cent.	1·060	0·991	1·016	0·870	0·786	0·792

These results are of particular interest, since Bloor (1916) could find no proof of a relation between high blood-fats and the presence of acetone bodies in the urine.

Blood-sugar. The most generally accepted index of the severity of a case of diabetes is the blood-sugar. 'The higher the blood-sugar the more serious the diabetes' (Joslin, 1923, b). A study of the blood-fat in relation to the blood-sugar is, therefore, of importance. This has been done in two ways, by observing the variations of the sugar and the fat in the blood of individual patients over periods of some weeks, and by calculating the average serum-fats of cases exhibiting certain blood-sugar percentages. The protocols of all the individual patients are too long to be quoted, and only three examples will be given.

Case S. M. Female, aged 59. Five years history of diabetes. Dieted for two years. No insulin.

Date.	Interval between exams.	Blood-sugar, mg. per cent.	Serum-fats, c.c. per cent.
15.3.32	—	176	0·52
26.4.32	6 weeks	150	0·84
24.5.32	4 „	89	0·80
31.5.32	1 „	128	0·88
13.6.32	2 „	115	0·72

Case V. J. Female, aged 21. Two years history of diabetes. Treatment on strict diet for one year. Insulin commenced during these observations. Concurrent hyperthyroidism.

Date.	Interval between exams.	Blood-sugar, mg. per cent.	Serum-fats, c.c. per cent.
19.4.32	—	207	1·32
26.4.32	1 week	117	1·08
10.5.32	2 weeks	89	1·36
31.5.32	3 „	187	0·92

Case P. P. Female, aged 59. Eight years history of diabetes. Treatment by diet and insulin for most of this time. Receiving 20 units of insulin per diem. No acetonuria but glycosuria present at each examination.

Date.	Interval between exams.	Blood-sugar mg., per cent.	Serum-fats, c.c. per cent.
8.3.32	—	178	0·74
5.4.32	4 weeks	300	0·76
19.4.32	2 „	187	0·74

Other results are in accordance with these and show (*a*) that there is no parallelism between the blood-sugar and the serum-fat concentrations, and (*b*) that the fluctuations of the serum-fats are less considerable than of the blood-sugar in any individual case. Gray (1924) likewise found that the stability of the blood-fat after treatment is greater than that of the blood-sugar. As far as possible, in the cases from which our deductions are drawn, the external influences on the blood-sugar have been controlled by enforcing a three hours' fast before the blood sample was taken, and it would so seem that any one isolated blood-sugar estimation is a less reliable means of judging the severity of a case of diabetes, than a single serum-fat determination would be.

A disparity between these two results is also evident in a table of averages :

Diabetic Cases (Male and Female) Grouped According to the Concentration of Blood-sugar at the Time of Estimating the Serum-fats.

Blood-sugar group mg. per cent.	No. of cases.	Average serum-fats c.c. per cent.
Less than 100 mg.	12	0·858
100–149	28	0·787
150–199	32	0·775
200–249	10	0·914
250–299	7	0·821
Over 300	3	0·933

Hyperthyroidism. One of the cases in this series was that of a girl whose diabetes was complicated by hyperthyroidism. This is the case V. J., quoted in the preceding paragraph. It is known that hyperthyroidism seriously aggravates diabetes (Wilder, 1926), but a decrease of the blood-fats is found in thyrotoxic cases uncomplicated by diabetes (Epstein and Lande, 1922). In this case, V. J., the serum-fats were persistently high, which is consistent with a severe case of diabetes, but inconsistent with simple hyperthyroidism, of which one such case showed the extremely low serum-fat content of 0·26 c.c. per cent. Wishnofsky and Byrom (1931) consider that the ultimate diagnosis of diabetes in a case showing increased thyroid activity, hyperglycaemia, and glycosuria rests in the respiratory quotient curve. A respiratory quotient that rises to 0·88 after absorption of an adequate amount of glucose is taken as evidence of a normal secretion of insulin. It would seem, however, that this diagnosis could be reached after a determination of the serum-fats by means of the Lipokrit. A serum-fat concentration exceeding 0·82 c.c. per cent. may be considered as strong evidence that the case is one of diabetes.

Discussion

These results, obtained by a new, simple, and apparently reliable technique, in general bear out the conclusions attained by other workers. Joslin, Bloor, and Gray, in 1917, published the results of blood-fat estimations made on 124 diabetic cases. Their findings led them to the conclusion that the blood-fats do not rise or fall with the changes in the blood-sugar, and that the blood-sugar is not nearly so accurate a test of the severity of a case of diabetes, measured from all points of view, as are the blood-fats. Cases with high blood-fats were regarded as presenting a less favourable outlook than cases with low blood-fats. By 1924, Gray had collected 1,000 cases of diabetes, on which blood-fat estimations had been made, and substantiated the opinions expressed in 1917. Gray, and later White (1925), point out the difficulty of correlating the concentration of fats in the blood with the clinical progress of the patient and with the possible influencing factors.

The series of cases presented here, though small, is enough to show that the serum-fats in diabetes behave in a manner very similar to that in which the fats of the whole blood behave. The serum-fats, although they do not correspond to the blood-sugar level, are high when the condition of the patient is severe, as is shown by their increase relative to the presence of glycosuria and acetonuria. Insulin in large doses produces a fall in the serum-fats, and it is probable that a high fat content of the serum is associated with a grave prognosis. Rabinowitch (1929) found that a high cholesterol content of the plasma indicates a grave prognosis in diabetes, and Bloor (1916) noted the parallelism of the cholesterol and total fat content of the blood in diabetic lipaemia.

The estimation of the serum-fats by this method may, therefore, prove of value to the clinician in the diagnosis, treatment, or prognosis of diabetes.

It remains only to discuss the possible explanations of the cause of the increase of fats in the blood in diabetes.

Three theories have already been advanced. The first, that the excess of fat arises from a fatty degeneration of the tissues, may be summarily dismissed in the light of more recent knowledge of the process of fatty degeneration. The second, that the fat in the blood-stream represents an accumulation of food-fat which the organism can no longer burn, cannot be supported in view of the work of Stewart, Gaddie, and Dunlop (1931), who showed that the diabetic can utilize fats, and of Marsh and Waller (1923), who proved that increase of food-fat did not necessarily lead to an increase of blood-fats. The third suggestion is that the lipaemia of diabetes is consequent upon the increased mobilization of depot-fat caused by the partial starvation. This factor cannot be ignored, for Mottram (1909) has clearly shown that starvation produces a mobilization of fat, stored in the connective tissue deposits, to the liver, and as we have pointed out above, it is

probable that the fats responsible for the increase in the blood in diabetes come from the depots.

There is yet a fourth explanation of diabetic lipaemia, which is dependent on there being a successful utilization of fats by the diabetic, and on there being an increase of fat in the blood corresponding to the impairment of carbohydrate metabolism, and a decrease with the improvement of carbohydrate metabolism, as following insulin. This explanation is as follows: as the catabolism of the carbohydrates is interfered with to a greater or lesser extent, so the mobilization of fats is provoked in order to meet the calorific requirements of the body, and as in the severer cases with absence of carbohydrate destruction oxidation of the fats is incomplete, some of the potential calories of the latter are lost and a still further supply of fats is demanded.

Summary and Conclusions

1. Rückert's haemolipokrit method for the volumetric estimation of fat in blood-serum is described, discussed, and recommended.

2. The result of serum-fat estimations on 103 diabetic and 55 non-diabetic blood samples are recorded.

3. Increase of the serum-fats is associated with the presence of glycosuria and acetonuria and with the clinically severer cases of diabetes in particular. But no clear relationship can be established between the serum-fat and the blood-sugar level.

4. There is no relation between the serum-fat and the body-weight of the patient.

5. A case of diabetes with hyperthyroidism is discussed, and the value of a serum-fat determination as an aid to diagnosis is suggested.

6. An opinion is expressed that the lipaemia of diabetes is solely dependent on the inhibition of carbohydrate metabolism, and that the increased amount of fat in the blood is evidence of a mobilization of fat in response to the calorific requirements of the body.

In conclusion, the writer wishes to express his gratitude to Professor J. H. Dible for his interest and advice throughout this work, and to Dr. H. S. Pemberton for permission to investigate the diabetic cases at his clinic at the David Lewis Northern Hospital, Liverpool, and to have access to his case records.

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DISEASES ASSOCIATED WITH PERNICIOUS ANAEMIA.[1]
(IN A STUDY OF 370 CASES).

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The association of pernicious anaemia with other diseases has been noted from time to time by various writers, and attempts have been made to link up the conditions through some common aetiological factor. In most cases the coexistence of two separate conditions has been readily detected, but occasionally the predominance of one disease has masked more or less completely the second coexisting condition.

A review of the first 370 consecutive cases of definite pernicious anaemia (with or without symptoms of cord involvement) in my own series has disclosed the fact that many conditions may precede, follow, or coexist with the pernicious anaemia in quite a fortuitous manner without any apparent relationship between them.

In this series there were 86 patients (23·2 per cent.) with pernicious anaemia having signs or symptoms of other conditions distinct from the Addisonian anaemia. These embraced 37 definite diseases or syndromes, and in eleven cases more than one of these coexisting diseases were present. Their distribution is shown in Table I.

I have omitted from consideration here postero-lateral sclerosis of the spinal cord without blood changes.

It will be seen that the main diseases associated with pernicious anaemia in this series show the following distribution :—pulmonary diseases 20, cardiovascular 17, endocrine 16, dermatoses 13, urinary 9, neoplastic 8, syphilis 6, gastrointestinal ulceration 2, and a miscellaneous group comprising parasitic infestation 2, diseases of the central nervous system (other than subacute combined degeneration of the spinal cord) 3, recurrent alveolar abscesses 1, and migraine 1.

The sex distribution in this group of 86 patients showed a proportion of females, 47 to males 39, giving a ratio of 1·20 to 1·0. This is in marked contrast to the figures for the whole series of 370 cases of pernicious anaemia in which the proportion was 186 females to 184 males, giving a ratio of 1·01 to 1·0. This increase in the female proportion is entirely due, as will be seen later, to a preponderance in the group with thyroid involvement,

[1] Received January 28, 1933.

and reference to the table shows that there were five times as many females as males in this section. In the other sections the sexes appear to be equally liable to coincident diseases with pernicious anaemia.

TABLE I

Diseases Co-existing with Pernicious Anaemia in a Series of 370 Cases

Diseases.	Number of cases.			Per cent. of whole series.
	Males.	Females.	Total.	
Pulmonary diseases (20)				
Asthma, bronchitis	7	6	13	3·51
Pneumonia	3	3	6	1·62
Tuberculosis	1	0	1	0·27
Cardiovascular (17)				
Hyperpiesis	4	4	8	2·16
Angina	3	0	3	0·81
Hemiplegia	0	2	2	0·54
Thrombophlebitis	1	1	2	0·54
Auricular fibrillation	0	1	1	0·27
Pericarditis	0	1	1	0·27
Endocrine (16)				
Exophthalmic goitre	1	4	5	1·35
Diabetes mellitus	2	2	4	1·08
Simple thyroid adenoma	0	3	3	0·81
Myxoedema	1	2	3	0·81
Hyperthyroidism	0	1	1	0·27
Dermatoses (13)				
Acne rosacea	2	1	3	0·81
Psoriasis vulgaris	2	1	3	0·81
Urticaria	1	2	3	0·81
Eczema	1	1	2	0·54
Leukoplakia	0	1	1	0·27
Pruritus vulvae	0	1	1	0·27
Urinary (9)				
Albuminuria	2	2	4	1·08
Cystitis	1	2	3	0·81
Nephritis	1	0	1	0·27
Haematuria	1	0	1	0·27
Malignant disease (8)				
Buccal epithelioma	2	1	3	0·81
Cervix, vagina	0	2	2	0·54
Stomach	1	1	2	0·54
Colon	0	1	1	0·27
Syphilis (6)	3	3	6	1·62
Gastro-intestinal ulceration (2)				
Stomach	0	1	1	0·27
Duodenum	0	1	1	0·27
Miscellaneous (7)				
Parasites	0	2	2	0·54
Diseases of C.N.S.	2	1	3	0·81
Recurrent abscesses	1	0	1	0·27
Migraine	0	1	1	0·27
	43	55	98	

Pulmonary Diseases

Twenty cases had diseases affecting the lungs—thirteen were subject to asthma or bronchitis, one developed acute phthisis, and six were admitted to hospital with pneumonia or developed it afterwards. Whilst asthma and bronchitis do not appear to have any influence upon the haemopoietic responses, pneumonia, influenza, and similar infections are particularly fatal in patients suffering from pernicious anaemia, for sepsis apparently inhibits the action of liver and stomach preparations upon the haemopoietic centres. Similar observations have been made by Gulland and Goodall (67), Zadek (203), Seyderhelm (163), Witts (199), Vaughan (181), and Smithburn and Zerfas (168) amongst others.

Of the six cases with pneumonia, five died within a few days of its onset, while one recovered. The latter had a blood count of red blood-cells, 3,500,000, and haemoglobin 82 per cent., and had been on desiccated hog's stomach for about one month previously as an out-patient. Four of the fatal cases had very severe degrees of anaemia and had not received previous treatment other than an occasional liver dietary. The fifth case had been under treatment with hog's stomach continuously for $3\frac{1}{2}$ years without any sign of relapse, and all of the monthly blood counts that were done during this period lay between 4·30 and 5·90 millions red blood-cells and 90–113 per cent. haemoglobin. He was admitted to hospital, however, on Jan. 6, 1933, and died twelve hours later from acute influenzal pneumonia of three days' duration: there were no signs or symptoms of anaemia.

Tuberculosis

The infrequency of active pulmonary tuberculosis amongst patients with pernicious anaemia has been so striking that many clinicians have commented upon the rarity of this combination (205), whilst some (38, 127, 165) have even considered that either disease confers upon its sufferer an immunity to the other. There appear, however, in the medical literature a relatively small number of definite cases of pernicious anaemia associated with tubercle (Table II), and a few others about which some doubts may exist as to the correctness of the diagnoses regarding the types of anaemia concerned.

On the other hand, Grezel (66) suggested that tuberculosis is a definite aetiological factor in pernicious anaemia; his work was criticized by Fingerhuth (51), who again emphasized the necessary criteria before a diagnosis of pernicious anaemia should be accepted. Kretz's case (95) had pulmonary tuberculosis with cavitation, together with fibrous stenosis of the intestine. I have described below the occurrence of pernicious anaemia following chronic intestinal stenosis or obstruction, but it has been observed that whilst many of those cases had purely fibrous stenoses without evidence of tuberculosis (*vide infra*)—others were definitely of a tuberculous nature

Table II

Pernicious Anaemia and Tuberculosis

Author.	Reference.	No. of cases.	Tuberculous condition.	Diagnosis confirmed.
Becker	8	1	Intestinal	Laparotomy resection
Berger	11	1	Pulmonary and miliary	Autopsy
Bloch	14	1	Pulmonary	Clinically *
Borchgrevink	17	1	Intestinal	Autopsy
Bretschneider	24	1	Intestinal (T.B. mesenteric glands)	,,
Campbell and Conybeare	26	1	Pulmonary	,,
Carnot and Jacquet	27	1	,,	,,
Dieballa	38	1	Chronic pulmonary	,,
Dubois	39	1	Pyloric glands	Laparotomy
Fiessinger and Moreau	50	1	Miliary	Autopsy
Freeman	52	1	Acute miliary	,,
Gluzinski	58	1	Intestinal	,,
Görander	59	1	Pulmonary	,,
Hills	77	1	Chronic glandular	,,
Karlmark, Olofsson	90	1	Miliary	,,
Keefer	91	1	Intestinal	Laparotomy
Kretz	95	1	Pulmonary (Cavitation) intestinal	Autopsy
Labbé	98, 102	1	Pulmonary	,,
Levin	107	2	,,	Clinically * and autopsy
Lubarsch	111	1	,,	Autopsy
Mathias	116	1	Chronic glandular	,,
Meissner	119	1	Pulmonary	,,
Meulengracht	120, 123	1	Intestinal	Resection and biopsy
Neuberger	131	1	Pulmonary	Radiologically and clinically *
Obrastzow and Wyssokowitsch	133	1	Subacute miliary	Autopsy
Pater, Rivet	136	1	Pulmonary	,,
Pissavy, Robine and Saxe	137	1	Mediastinal and mesenteric glands	,,
Qvarnström	143	5	?	,,
Strandell	172	1	Small intestine, pulmonary	,,
,,	172	2	Pulmonary	,,
Szczepanski	174	1	Intestinal	,,
Tillgren	177	1	?	,,
Walterhoefer	184	1	?	,,
Wilkinson	This series	1	Acute pulmonary	Radiologically and clinically *
Zadek	203, 204	3	Intestinal (transverse colon 1; small intestine 2)	Autopsy

* Tubercle bacillus present in sputum.

(206). Dubois' case (39) is noteworthy since pernicious anaemia apparently developed in a child following pyloric obstruction by tuberculous glands; this, of course, is not difficult to understand in view of the present views regarding the gastric deficiency that exists in patients suffering from pernicious anaemia, but this case is of peculiar interest, insomuch as it occurred in a child rather than an adult, the occurrence of pernicious anaemia below the age of 25 years being of extreme rarity. In my series of cases only one was found to have acute pulmonary tuberculosis, and this apparently developed after a complete remission of the pernicious anaemia had continued for two years.

A labourer, aged 60 years, was admitted to hospital on 14.5.30 complaining of increasing weakness and shortness of breath on exertion during the previous nine months, paraesthesiae in fingers and toes, anaemia, and loss of weight and appetite. There was no complaint of sore tongue, indigestion, flatulence, or chest trouble, and the bowels had been quite normal. There was no relevant previous medical history. His father died following rheumatic fever, a sister died of anaemia at 30 years of age, and a brother died following a gastric ulcer; another sister was well.

Examination. Slightly built edentulous man, weight 8 st. 10 lb., smooth shiny skin, yellow sclerotics and mucous membranes, with marked malar flush, white hair. The liver and spleen were not enlarged; nervous reflexes present and brisk; nothing else abnormal to be found.

Blood count. Red blood-cells, 2,350,000; white blood-cells, 2,500; haemoglobin 52 per cent.; colour index 1·3. Fractional gastric analysis—achylia gastrica. Wassermann reaction negative.

He was given desiccated stomach powder (28 grm. daily) and hydrochloric acid. There was a rapid response, and he was discharged from hospital (9.7.30) with a count of—red blood-cells, 4,420,000; white blood-cells, 8,400; haemoglobin 108 per cent. He returned to work and remained very well on a maintenance dose of 14 grm. desiccated stomach powder daily; the blood counts varied at monthly intervals for nineteen months between—red blood-cells, 4·5–5·8 millions, haemoglobin, 80–108 per cent. On 11.2.32 he had a count of red blood-cells, 4,500,000; haemoglobin 84 per cent.; white blood-cells, 7,600, appeared to be quite well, and did not complain of any symptoms. He did not attend again for four months, when he gave a history of sudden pain in the epigastrium that 'caught his breath', cough with much sputum, flatulence, together with sudden marked loss of weight and strength. There was no complaint of sore tongue, indigestion, anaemia, or paraesthesiae.

Examination showed much general wasting, marked malar flush and definite evidence of active pulmonary tuberculosis in both lungs. Radiological examination of chest confirmed 'extensive disease involving most of the left lung and the upper lobe of the right lung'. Tubercle bacilli were present in the sputum.

The blood count at this time was—red blood-cells, 3,600,000; haemoglobin 68 per cent.; white blood-cells, 12,000; colour index, 0·95; polymorphonuclears, 85·5; lymphocytes, 8·25; large mononuclears, 6·25; no eosinophils or basophils; abundant platelets; some aniso- and poikilocytosis.

The fatal termination occurred ten weeks later, no autopsy being obtained.

Cardiovascular

Seventeen cases (4·6 per cent. of the total series) had definite symptoms falling under this heading. It is a common experience to find that patients with pernicious anaemia complain of cardiac pain—an observation that has been clearly noted by Coombs (33), and Herrick and Nuzum (76). Willius and Giffin (197) observed the occurrence of varying degrees of angina in 2·7 per cent. of their cases of pernicious anaemia.

In the present series three cases (all males aged 60, 67, and 72 years respectively) had definite symptoms of angina or coronary thrombosis, and two died following attacks, although their blood pictures had become normal (only one had a raised blood-pressure of 190/96). Eight others (four males, aged 45, 56, 59, and 60 years, and four females aged 59, 60, 62, and 66 years respectively) complained of pseudo-anginal symptoms with pain in the praecordial area. These latter all had raised blood-pressures (150/80, 170/105, 170/90, 188/124, 190/96, 202/112, 214/90, 240/144) in contrast with the first three.

Hyperpiesis appears to be the commonest condition in this section, and the usual symptoms associated with it have been vertigo, headaches and vague, sometimes acute, pseudo-anginal pains in the chest. The pain may be over the praecordia with some tendency to radiate to the shoulder, or it may be of a 'gripping' sensation as though the chest were in a vice. This symptom, of course, is quite distinct from the pain often accompanying gastro-intestinal flatulence and relieved by hydrochloric acid and pepsin (193). Treatment of the anaemia with stomach and liver preparations has not had any marked effect upon the raised blood-pressures in these cases, which have otherwise regained normal health and blood pictures.

Thrombophlebitis has been described by Spence (169) as a sequela of the liver treatment for pernicious anaemia, while one of Wright's cases (200) died from a pulmonary thrombosis. I have already reported one case of femoral thrombosis (192), and quite recently I have seen a second case of bilateral femoral thrombosis in a case of pernicious anaemia that was admitted to hospital and recovering from pneumonia.

There were also in this group one case each of auricular fibrillation, pericarditis, and two with histories of hemiplegia. One of the latter cases is of interest in that, early in the treatment the patient suffered a sudden paresis of the right arm and hand and slight involvement of the facial muscles with loss of speech—this subsidiary complaint has shown marked improvement since.

Coombs (33) has described the occurrence of aortic disease in association with pernicious anaemia, but no such cases were found in my series.

Diabetes Mellitus

The first case of pernicious anaemia associated with diabetes mellitus was described by Parkinson (135) in 1910, and comparatively few such

cases have been reported since then. Thus, only eighteen cases are to be found in a total of 10,038 patients with diabetes mellitus (0·18 per cent.), and but fifteen in a series of 2,461 with pernicious anaemia (0·61 per cent.) occurring in the combined series of Adams (1), Giffin and Bowler (56), Goudsmit (61), Joslin (88), Murphy and Moxon (130), Wright (200), and Wilkinson (present series). Other cases have also been reported from time to time; thus Root (148) collected twenty cases from the New England Deaconess Hospital records and other unpublished sources to which may be added further cases by Adams, three (2), Tillgren, two (177), and one each by Arnzten (3), Baumgartner (7), Berghausen (12), Bowen (20), Chvostek (31), Hitzrot (79), Meulengracht (124), Parkinson (135), Schuman (161), Shookhoff (166), Wright (200), and Yong (201), making a total of sixty patients recorded in the medical literature as suffering from pernicious anaemia and diabetes mellitus simultaneously.

TABLE III

Coexisting Pernicious Anaemia and Diabetes Mellitus

Author.	Reference.	Diabetes mellitus.		Pernicious anaemia.	
		Cases with pernicious anaemia.	Number examined.	Cases with diabetes mellitus.	Number examined.
Adams	1	3	2,000	3	1,000
Giffin, Bowler	56	—	—	1*	628
Goudsmit	61	5	1,650	5	379
Joslin	88	5	5,086	—	—
Murphy, Moxon	130	3	827	—	—
Wilkinson	This series	—	—	4	370
Wright	200	2	475	2	84
		18	10,038	15	2,461

* One other had only a transient glycosuria.

In two cases, not included above, one had only a transient glycosuria (56) while the other had a normal gastric secretion and would appear to be a case of haemolytic anaemia (166); on the other hand observers (21) have commented on the non-occurrence of pernicious anaemia in large series of cases of diabetes mellitus.

In my series of pernicious anaemia I have only found four cases (1·08 per cent.) suffering from both diabetes mellitus and pernicious anaemia. Of these, two (one male; one female) had had diabetes several years before the onset of pernicious anaemia, one male had had pernicious anaemia three and a half years before the diabetes which developed during a remittant stage of the anaemia, and the fourth (female) was admitted to hospital in a state of diabetic coma with co-existing pernicious anaemia. The ages of these patients were 35, 66, 55, 52 years respectively.

All four were admitted to hospital with the typical symptoms and blood pictures of Addisonian anaemia.

Three are now quite well on suitably adjusted diets without insulin, but

including one ounce daily of desiccated hog's stomach (Boots 'Pepsac') the fourth did not recover from the diabetic coma.

It is interesting to note that there was quite frequently in my series a history of diabetes mellitus in other members of families in which pernicious anaemia existed—this has been observed by others (61, 148). The familial tendency of pernicious anaemia has, of course, already been commented upon in a previous paper (194), while diabetes mellitus itself is also known to show a similar familial tendency (88).

The following brief notes illustrate the onset and occurrence of pernicious anaemia and diabetes mellitus in one case.

A joiner, aged 55, was admitted to hospital in May 1928 complaining of loss of weight, indigestion, flatulence, occasional vomiting, and during the previous four weeks a noticeable increase in pallor, dyspnoea, palpitation on exertion, soreness of the tongue with slight dysphagia.

There was nothing relevant in the familial or previous medical histories.

Examination. A fairly well-nourished man, 8st. 6lb.; marked pallor of the mucous membranes and skin; slight glossitis; artificial dentures, except for two carious teeth. There was nothing abnormal in the heart, lungs, or abdomen; the nervous reflexes were present and normal. Wassermann and van den Bergh reactions negative.

Blood count. Red blood-cells, 1,580,000; white blood-cells, 4,600; haemoglobin, 46 per cent.; colour index, 1·5; scanty platelets, marked aniso- and poikilocytosis, normoblasts and megaloblasts present. Fractional gastric analysis showed achylia gastrica.

He was given fresh liver (180 grm.) daily together with a mixture of hydrochloric acid and pepsin. He showed a good response and was discharged with a blood count of:—red blood-cells, 3,260,000; haemoglobin, 78 per cent.; colour index, 1·2.

He continued to take lightly cooked fresh liver (120 grm. daily) with the acid mixture, and when next seen (9.3.29) had red blood-cells, 5,670,000; haemoglobin, 102 per cent.; white blood-cells, 8,000; colour index, 0·9. This blood condition was maintained, but on 10.10.1931 he complained for the first time of the sudden onset of a dry mouth associated with considerable thirst, some loss of weight and strength and polyuria. There was glycosuria.

Blood-sugar—0·345 grm. per 100 c.c.; blood count—red blood-cells, 5,100,000; white blood-cells, 8,400; haemoglobin, 100 per cent.; colour index, 1·0.

He was readmitted to hospital for adjustment of diet.

His weight was 9st. 3lb.; tongue smooth, moist and deeply fissured. There were no abnormalities in the heart, lungs, abdomen, and nervous system.

The diet was adjusted, without the necessity for insulin, to a total of 2,115 calories. This included the requisite maintenance dose of desiccated hog's stomach (7 grm.) necessary for the coexisting pernicious anaemia. He was discharged on this dietary without insulin or liver, and has continued well since.

The present condition (11.1.33) shows—red blood-cells, 5,050,000; white blood-cells, 6,700; haemoglobin, 102 per cent.; colour index, 1·01. Blood-sugar—0·109 grm. per 100 c.c.; urine, sugar free and normal.

Diseases of Thyroid Gland

Twelve cases of pernicious anaemia had histories of thyroid gland involvement—exophthalmic goitre 5, thyroid adenoma 3, myxoedema 3, and 1 with hyperthyroidism without exophthalmos.

It has several times been pointed out that anaemia (usually of the so-called 'secondary' type) may be associated with diseases of the thyroid gland (113, 122, 123, 124, 167, 170).

Cases, however, have been reported having blood pictures characteristic of pernicious anaemia. Thus, Kerppola (92), Giffin and Bowler (56), Means, Lerman, and Castle (117), Boothby (15, 16), and Meulengracht (122) all quote cases of pernicious anaemia associated with myxoedema, while Hanssen and Stub (71), Reinhold (144), and Meulengracht (124, 125) amongst others refer to cases complicated by hyperthyroidism.

It has been suggested that the thyroid secretion plays some part in haemopoiesis (114), but there is little evidence in favour of this as an hypothesis for the coexistence of pernicious anaemia with diseases of the thyroid gland. On the other hand, achlorhydria is to be found in pernicious anaemia and quite frequently in thyroid dysfunction, but it is difficult to prove the importance of this as a common aetiological factor.

Ordinarily the basal metabolic rate in cases of pernicious anaemia has been considered to be within the normal range or slightly elevated (16, 115, 126, 147, 178), so that marked alterations in this would suggest involvement of the thyroid gland; but it should be noted that Suzman (173) has suggested very recently that the basal metabolic rate may be greater than plus 20 per cent. in 18·5 per cent. of cases uncomplicated by spinal cord involvement, and minus 20 per cent. or less in 10·8 per cent. of cases showing spinal cord involvement.

In the cases quoted in this series the basal metabolic rates varied from plus 110 per cent. in the case with acute Graves' disease to minus 46 per cent. in the worst case of myxoedema. Of the five with exophthalmic goitre, two had developed the condition subsequent to the diagnosis of pernicious anaemia. One is of considerable interest since an acute, fulminating exophthalmic goitre developed during a remission of the anaemia within a period of a few weeks, although the patient had been under constant supervision for nearly three years.

A similar case of malignant fulminating type of Graves' disease with a basal metabolic rate of plus 200 per cent. unassociated with pernicious anaemia has been described by Carnot, Benard, Rudolf, and Veran (28), who recommended the administration of iodine and avoidance of surgical intervention during such hyperacute stages.

In the following case good results have followed a two-stage thyroidectomy.

A housewife, aged 40 years, was admitted to hospital on 26.8.30 complaining of anaemia, shortness of breath, lack of energy, palpitation, slight

paraesthesiae in hands and feet, and severe headaches. She had had persistent nausea, vomiting, and diarrhoea for the seven days prior to admission, followed by stiffness and a feeling of tightness in the legs; but there was no history of sore tongue, or loss of weight.

The menses were quite normal and regular. There was nothing relevant in the previous medical history. Her father died of pneumonia, her mother following parturition; she had two sisters, one brother, and two children, all well.

On Examination. A slightly-built and edentulous woman with no obvious wasting, very anaemic, and the skin and mucosae were of a lemon-yellow colour; she was in a very poor condition; tongue pale, swollen, glazed, and painless.

There were no marked abnormalities in the lungs, abdomen, and heart; ankle- and knee-jerks present and normal; superficial abdominal reflexes were absent; plantar responses flexor, vibration and joint sense impaired in both legs.

Blood count. Red blood-cells, 1,512,000; haemoglobin, 40 per cent.; colour index, 1·3; platelets scanty; aniso- and poikilocytosis very marked; megaloblasts, nucleated red cells, present.

Blood group IV; Wassermann reaction negative.

Gastric analysis showed achylia gastrica.

She was treated with 30 grm. of desiccated hog's stomach daily, and responded excellently, so that she was discharged from hospital on 20.10.30 with a blood count of red blood-cells, 4,400,000; white blood-cells, 4,000; haemoglobin, 93 per cent.; colour index, 0·96.

She attended this clinic regularly, and a full blood count was done every four weeks during the subsequent two years. During that time the red blood-cells and haemoglobin were always between 4·2 and 5·6 millions and 86 and 96 per cent. respectively.

On 3.8.32 she complained of a sudden enlargement of the thyroid gland that had occurred since she had attended four weeks previously. This was associated with the onset of marked nervousness and tremor of the hands, so that she was unable to hold anything without dropping it; there was no palpitation on exertion.

Examination showed considerable bilateral exophthalmos, tremor of the hands, and an enlarged thyroid gland, the right lobe being greater than the left. The patient had obviously developed a very acute Graves' disease. There were no signs of anaemia.

The blood count was: red blood-cells, 4,620,000; haemoglobin, 86 per cent.; white blood-cells, 6,400; colour index, 0·93.

The basal metabolic rate was plus 110 per cent.

She was admitted as an urgency, and a hemithyroidectomy was carried out by Mr. P. R. Wrigley, F.R.C.S. (to whom I am indebted for permission to refer to his notes) on 24.8.32, with much improvement in the condition of the patient, her weight increasing and the exophthalmos and nervousness diminishing markedly.

On 24.11.32 the basal metabolic rate was plus 72 per cent. and blood count: red blood-cells, 5,110,000; haemoglobin, 88 per cent. The second stage, completing the thyroidectomy, was carried out successfully on 30.11.32.

Throughout the whole time (except the two days following operation) the patient was kept on 30 grm. of desiccated hog's stomach (Boots) daily, without any relapse in the blood condition, and she was discharged from

hospital on 8.12.32. At the time of writing she has shown considerable further improvement.

The remaining three cases with exophthalmic goitre developed pernicious anaemia at periods of three, five, and twelve years respectively after radiation treatment had been administered for the thyroid condition. Varying degrees of exophthalmos were present on admission to hospital for treatment of the pernicious anaemia.

Of the three women with simple thyroid adenomata one had had these since childhood, one since puberty, and one for at least four years before pernicious anaemia had been first diagnosed at the respective ages of 48, 52, and 65 years.

Myxoedema was diagnosed in two women and one man after admission to hospital (basal metabolic rates: minus 26, minus 49, and minus 46 per cent. respectively), and they have responded well to combined treatment with hog's stomach and thyroid medication, the basal metabolic rates of these cases returning to approximately normal limits (plus 10, plus 16, and minus 2 per cent. respectively).

Only one case of hyperthyroidism, associated with pernicious anaemia, has been observed, and it has not been possible to determine the time of initial onset with respect to the anaemia. On admission to hospital the basal metabolic rate was plus 31 per cent., and the patient has responded extremely well to intravenous liver and oral iodine therapy. She is now in normal health and free from symptoms and signs of either disease with a basal metabolic rate of plus 15 per cent.

It is noteworthy that the sex ratio in this group of cases is quite disproportionate to the usually-occurring general ratio amongst cases of pernicious anaemia. Thus there are eleven females and two males, and this is in accord with the commonly observed sex occurrence associated with diseases of the endocrine system.

Dermatoses

Thirteen cases of pernicious anaemia had the following skin affections—acne rosaceae 3, psoriasis vulgaris 3, urticaria 3, eczema 2, leukoplakia 1, pruritus vulvae 1. It is interesting to speculate upon the significance of the associated achlorhydria, for it has been shown that gastric secretory impairment, often to the extent of complete achylia, occurs in many cases of acne (25, 150, 151, 196), psoriasis vulgaris, and urticaria (189, 196), while disordered metabolism has formed the basis of theories to explain such dermatoses. I have considered the question more fully in another place (196). The three urticarial cases are of considerable interest in so much as the skin condition in each case could be attributed directly to (i) fresh liver diet (probably associated with lack of hydrochloric acid secretion; (ii) lack of hydrochloric acid and pepsin; (iii) hydrochloric acid and pepsin therapy respectively, and was relieved in these cases by treatment with hydrochloric

acid and pepsin, and discontinuance of liver diet in case (i), by the administration of hydrochloric acid and pepsin in case (ii), and the discontinuance of hydrochloric acid and pepsin therapy in the third case.

One case developed a persistent pruritus vulvae subsequently to the onset of the remission in her pernicious anaemia. No difficulty was encountered in diagnosing the anaemia, although Schulze (160) describes the case of a woman of 63, whose first symptom was pruritus vulvae, which disappeared rapidly and completely after the institution of liver treatment.

Urinary

Four cases had marked albuminuria when admitted to hospital, but only one of these has shown a persistence of the condition without diminution during five years after successful treatment of the pernicious anaemia; the urines of the other three are now free from albumin. Only one case of chronic nephritis has been observed, and it was found in a man who had been receiving regular courses of intensive arsenical treatment for the pernicious anaemia; there was also a very marked pigmentation of the skin that was due most probably to the same cause. Renal lesions, in association with pernicious anaemia, have been noted by Labbé and others (98, 101, 102) and v. Noorden (132), while Davidson, McCrie, and Gulland (35) reported the occurrence of acute nephritis and uraemia following liver treatment, but I have not yet observed it after stomach therapy.

It is a common observation that the presence of sepsis or infection renders the prognosis and response to treatment in such cases of pernicious anaemia less certain (*vide supra*, p. 283), thus cystitis and cystopyelitis become complications of first importance (6). Three cases in this series came under observation with a complicating cystitis or cystopyelitis, which showed improvement after suitable vigorous treatment; subsequently the anaemia showed a marked acceleration in the rate of remission.

One patient with paroxysmal haematuria was subject to attacks after exposure to cold and wet in the winter time; he was a road navvy. Complete investigations (other than surgical exploration) have failed to disclose any organic cause for the condition, and little physical discomfort now occurs. The pernicious anaemia has been kept under complete control with the aid of desiccated stomach powder (Boots) for the last three years without relapse.

Malignant Disease

Eight cases in this series (Table I) have also had malignant disease (Table IV); in three, pernicious anaemia was the initial disease, while two commenced with the malignant condition and three apparently began with both conditions simultaneously. Of these, two (one male, one female) had gastric carcinoma, three (two males, one female) buccal epitheliomata with secondary cervical glands; two women had uterine carcinomata, and one woman had a malignant involvement of the colon.

Table IV

Pernicious Anaemia and Malignancy (Wilkinson)

Case.	Sex.	Age.	First disease diagnosed.	Neoplasm and site.	Confirmed at	Gastric analysis.	Interval between diagnosis of two conditions.	R.B.C.s $\times 10^6$.	H.B. %.	C.I.	Platelets.	Megaloblasts, normoblasts.
A	M	39	P.A.	Gastric carcinoma	Autopsy	Achylia	5 years	2·00	46	1·15	very few	present
B	F	43	?	Gastric carcinoma	Laparotomy	Achylia	—	2·20	58	1·30	very few	present
C	F	55	P.A.	Uterine carcinoma	Examination	Achylia	9 months	2·00	42	1·05	very few	present
D	F	46	?	Uterine carcinoma	Examination	—	?	0·64	15	1·25	very few	present
E	M	59	P.A. and S.C.D. cord	Epithelioma fauces	Operation	Achylia	2¼ years	4·00	104	1·30	diminished	present
F	F	55	Epithelioma	Epithelioma tongue	Operation	Achylia	4 years	1·00	26	1·24	very few	present
G	M	59	Epithelioma	Epithelioma floor of mouth	Operation	Achylia	10 months	2·00	44	1·15	very few	present
H	F	67	?	Splenic flexure colon	Clinically, radiologically	Achylia	—	1·60	40	1·25	very few	present

The first two cases resemble that reported by Plummer (138), and the man (Case A) is interesting in that he had been under treatment for pernicious anaemia for some five years prior to the onset of the gastric carcinoma, which had a singularly rapid onset and progress. The case has been fully reported elsewhere (191).

He was first seen in 1926, when a diagnosis of pernicious anaemia was made, and he remained perfectly well and in good health, doing his full-time work on a diet containing fresh liver with the addition of hydrochloric acid and pepsin. He was admitted to hospital in 1931 suffering from an advanced inoperable gastric carcinoma, and this was confirmed at autopsy.

The second (Case B) had an inoperable gastric carcinoma with achylia gastrica, and a typical blood picture for pernicious anaemia (red blood-cells, 2,200,000; haemoglobin, 59 per cent.; colour index, 1·3; aniso- and poikilocytosis; normoblasts and megaloblasts present), but there was a positive Wassermann reaction. She had been seen two years previously, when she had achylia gastrica, a positive Wassermann reaction, but a microcytic anaemia (red blood-cells, 3,320,000; haemoglobin, 49 per cent.; white blood-cells, 4,900; colour index, 0·6; no normoblasts or megaloblasts; some aniso- and poikilocytosis).

Of the two cases (C and D) of pernicious anaemia associated with uterine carcinoma, one appears to have had an approximately simultaneous onset of the two conditions, while the second case only showed the anaemia after the uterus and vagina had developed very septic conditions. The first case responded excellently to suitable treatment, and is now in perfect health; the latter did not respond to treatment, probably on account of the severe sepsis.

In connexion with the three cases (E, F, G) with buccal epitheliomata (one faucial; one lingual; one floor of mouth; all with secondary cervical glands), one had a previous history of anaemia, while the other two developed pernicious anaemia four years and four months respectively after surgical treatment and the implantation of radium emanation. These cases have been reported elsewhere (191).

Case H is of much interest, since a typical blood picture, characteristic of pernicious anaemia, was found and persisted, giving the usual reticulocyte response and haematological improvement on desiccated stomach therapy, despite the fact that clinically and radiologically she had a malignant involvement of the splenic flexure of the colon, causing chronic obstruction. The case is discussed below.

Comparatively few cases of pernicious anaemia have been reported in association with malignancy, and of these only thirty (excluding my own cases described herein) appear to have been definite cases of pernicious anaemia, in which an unsuspected malignant condition of the stomach has been found at autopsy or laparotomy (Table V); but five patients showed renal involvement (one; 14), uterine carcinoma (two; 78, 152), pancreatic carcinoma (one; 56) and primary carcinoma of the gall-bladder (one; 68).

In a few cases quoted in the medical literature important data are lacking, and the diagnoses are therefore not conclusive. For this reason care is required in accepting such as true cases of pernicious anaemia, since it has been shown that blood pictures resembling Addisonian anaemia may occur in cancerous conditions (207), while tumours of the bone-marrow may produce similar results (208).

TABLE V

Pernicious Anaemia and Malignant Disease (without Gastric Resection)

Author.	Reference.	No. of cases.	First disease identified.	Site of neoplasm.	Neoplasm confirmed at
Bloch	14	1	P.A.	Stomach	Autopsy
,,	,,	1	P.A.	Left kidney	,,
Borovanská-Felklová	19	1	P.A.	Stomach	,,
Brandes	22	2	P.A.	,,	,,
,,	,,	2	Cancer	,,	,,
Engel	44	1	Cancer	,,	,,
Garvey and Stern	54	1	P.A.	Pylorus	Operation
Gerhardt	56	1	P.A.	Pancreas	Autopsy
Haden	68	1	Cancer	Gall-bladder	,,
Hirschfeld	78	1	P.A.	Cervix	,,
Israël	87	1	P.A.	Stomach	,,
Lazarus	105	2	P.A.	,,	,,
Lubarsch	111	3	P.A.	,,	,,
Morawitz	127	1	P.A.	,,	,,
Plummer	138	1	P.A.	,,	Laparotomy
Porges	141	1	P.A.	,,	Autopsy
Rink	146	1	P.A.	,,	,,
Saltzman	152	1	Cancer	Uterus	Operation
Strandell	172	4	P.A.	Stomach	Autopsy (3) and laparotomy (1)
Waterfield and Shackle	185	1	P.A.	,,	Laparotomy
Wilkinson	This series	1	P.A.	,,	Autopsy
,,	,,	1	?	,,	Laparotomy
,,	,,	1	?	Colon	Clinically, radiologically
,,	,,	2	P.A.	Uterus	Examination
,,	,,	1	P.A.	Fauces	Operation
,,	,,	2	Epithelioma	Buccal cavity	,,
Zadek	202	2	P.A.	Stomach	Autopsy

Only a very few patients indeed have been noted in which neoplastic changes have been observed to develop, and been diagnosed during life, following a previously diagnosed and treated pernicious anaemia; three such have now been reported, the first two by Strandell (172) and Plummer (138) and the third by myself (191); in all the gastric carcinomata occurred during remissions following liver or stomach treatment.

The rarity of this latter association in the past was to be anticipated before the introduction of the liver and stomach treatments for pernicious anaemia owing to the almost invariable and rapidly fatal nature of this disease. With adequate modern treatment, however, the increased expectation of life for these patients with pernicious anaemia render it probable

that malignant disease will have an incidence amongst these patients at least equal to that for the ordinary population. Pernicious anaemia, in association with malignancy in other parts of the body, does not appear to have received much attention.

In these cases already quoted no obvious cause appears to exist for the association of the two conditions of which either may appear first in the patient.

TABLE VI

Pernicious Anaemia following Gastric Resection for Malignant Disease of the Stomach

Author.	Reference.	No. of cases.	Neoplasm confirmed at.
Berger	11	1	Gastrectomy
Breitenbach	23	1	,,
Ellis	43	1	,,
Hartman, H. R.	72	1	,,
Hochrein	80	1	,,
Hurst	86	3	No details
Meinertz	118	1	Gastrectomy
Morawitz	127	1	,,
Ungley	180	1	,,

On the other hand, there is a second group of cases in which the malignant condition has always preceded the pernicious anaemia; the eleven patients shown in Table VI developed the anaemia following previously performed partial or total gastrectomy for gastric carcinoma, and a similar incidence has been observed following gastrectomy or gastro-enterostomy for ulceration, multiple gastro-intestinal anastomoses (49, 110), and chronic intestinal obstruction (*vide infra*, p. 301). These cases are due probably to the removal, destruction, or impairment of the secretory functions of the stomach, thereby producing a deficiency of the antipernicious anaemia factor 'haemopoietin' (195) or 'intrinsic factor of Castle' (29) or else defective absorption of the products of normal gastric digestion, and they have most probably no causal origin in the malignant condition *per se*. In such patients there has usually been a latent period of some years (149, 182), Ellis (43) reporting one seventeen years later.

Eisen (41) has suggested that cancer of the stomach is associated with an anaemia which is more severe than that accompanying cancer in any other portion of the gastro-intestinal tract or other parts of the body. This is not supported by the figures for my cases (Table IV), and it is more probable that the degree of anaemia depends on the duration of the two diseases before coming under observation.

Syphilis

Six patients (three males, three females) had histories of syphilitic infection and were the only ones in the series to return positive results for the Wassermann reactions. In five cases the responses to combined treatment

with hog's stomach and antisyphilitic therapy were very satisfactory with a return to the normal blood picture. In one of the patients the infection was acquired some two years after the diagnosis of pernicious anaemia had been made. It is interesting in this respect to compare the case reported by Poole and Foster (140) of megalocytic anaemia following gastrectomy for syphilitic granuloma, and that of Rowlands and Simpson (149) for gastric ulcer with syphilitic gastritis. The occurrence of syphilis in association with pernicious anaemia or a megalocytic anaemia has of course been noted by others (209), although relatively little attention appears to have been paid to this combination.

In this connexion the following case is noteworthy:—

A copwinder, aged 40 years, attended the Out-patients Department of the Manchester Royal Infirmary on 3.2.31 complaining of a two years' history of epigastric pain, indigestion, nausea and vomiting without any relationship to the taking of food. Her appetite was poor, she had lost some weight, and was anaemic; the bowels were regular, and although there was no history of sore tongue, she had had some smarting in the tongue which was glossy, pale, and fissured; she also had menorrhagia and occasional oedema of ankles. Apart from a left oophorectomy in 1926 she did not furnish any other previous or family medical history. She had one child, no miscarriages.

Examination showed a fairly well-built pale woman with very septic teeth, superficial glossitis, and slightly enlarged spleen palpable on deep inspiration. The knee-jerks were absent, otherwise there was nothing else to be found clinically. Fractional gastric analysis showed achylia gastrica, lactic acid absent. Radiological examination of the gastro-intestinal tract was negative. The blood count on 4.2.31 was—red blood-cells, 3,220,000; white blood-cells, 4,900; haemoglobin, 49 per cent.; colour index, 0·6; polymorphonuclears, 78·75; lymphocytes, 12·25; large mononuclears, 8·25; eosinophils, 0·25; basophils, 0·5; aniso- and poikilocytosis marked; no normoblasts or megaloblasts; platelets abundant.

Wassermann reaction strongly positive in 1 in 40 dilution. She was referred to the V. D. Department, where she received antisyphilitic treatment until 17.11.32, when she developed intolerance to this therapy and a more marked anaemia. She was admitted to hospital complaining of a gnawing aching pain in the epigastrium with irregular attacks of pain made worse by food which often induced vomiting—these symptoms were of different character to the original ones two years previously.

Examination showed pale yellowish skin and mucosae, general emaciation of the body, and a large tender palpable mass in the mid-epigastrium: knee-jerks were absent, spleen and liver not definitely enlarged; nothing else abnormal.

The blood count (17.11.32) was—red blood-cells, 2,214,000; white blood-cells, 4,200; haemoglobin, 52 per cent.; colour index, 1·5.

Wassermann reaction—still positive in a dilution of 1 in 40.

Radiological examination. 'The lumen of the stomach in the middle third is narrowed, and on the lesser curvature below this is a filling defect which corresponds to the palpable mass. No peristalsis was observed over this region. The stomach was empty at five hours. Summary: There appears to be infiltration of the stomach walls over a large area ?specific, ?neoplastic.'

The interesting points about this case were the achylia gastrica, and microcytic anaemia with positive Wassermann reaction observed two years previously, suggesting syphilitic gastritis and anaemia. Subsequently, anti-syphilitic treatment over this period failed to cure or relieve the condition, while a macrocytic hyperchromic anaemia developed with an obvious gastric tumour, which was found on laparotomy to be a large inoperable gastric carcinoma.

As has been frequently observed, syphilis is usually associated with a microcytic type of anaemia as occurred at first in this case. With the onset of malignancy or possibly antisyphilitic treatment (although since arsenic was used one would have anticipated the reverse result in view of its use in the treatment of pernicious anaemia) the megalocytic type of blood picture developed—this association has already been discussed above (p. 292). It is of course not possible to ascribe its occurrence definitely to either the syphilitic or malignant condition—it may be coincidence, or due to possible bone-marrow metastases.

Gastro-Intestinal Ulceration

The occurrence of pernicious anaemia has been described following partial or total gastrectomy (210) and gastro-enterostomy (211) for gastric or duodenal ulceration, while a ' severe ' anaemia has also been observed under similar circumstances. The case reported by Fairley and Kilner (49) showed a megaloblastic anaemia following the development of a gastro-jejuno-colic fistula, subsequently to a gastro-jejunostomy for non-malignant pyloric obstruction. This occurrence of an anaemia of the Addisonian type has also been shown to follow chronic intestinal obstruction (*vide infra*, p. 301).

Morley (128), Lake (103), Berg (10), Henschen (75), Strauss (171), Gordon-Taylor and colleagues (60) amongst others, on the other hand, did not observe the occurrence of pernicious anaemia following gastrectomy in their combined series of cases, but some 40–50 per cent. of the patients subsequently showed ' secondary ' types of anaemia.

Davidson's case (34) is interesting in that there was free hydrochloric acid in the gastric secretion even after the diagnosis of pernicious anaemia. This point has been discussed in another place (190).

The two patients seen in this group of my series were both women (aged 34 and 46 years respectively) who had attended the clinic complaining of severe anaemia of the Addisonian type eleven and seven years respectively following gastric operation for ulcer.

A housewife, aged 34, had been admitted to hospital on 21.7.21 with a two years' history of epigastric pain commencing two hours after food; the attacks had become worse and were almost continuous. There had been three to four recent attacks of vomiting with slight amounts of blood in the vomitus. Only slight relief was gained after taking hot water or food and

she had lost weight from 9 st. 9 lb. to 8 st. during that period. She had received medical treatment for a similar attack sixteen years previously, and had always had some indigestion off and on since then.

After admission she had had an attack of haematemesis vomiting about three ounces of blood.

Radiological examination (27.7.21) showed the presence of a small ulcer on the lesser curvature of the stomach.

She had been operated upon (11.8.21) with the disclosure of a fair-sized ulcer on the posterior wall of the stomach one inch from the lesser curvature about the junction of the middle and upper thirds of the stomach, the ulcer being slightly adherent to the pancreas across the lesser sac. A Polya hemi-gastrectomy and gastro-enterostomy were performed with an excellent recovery.

In 1922 (November 3) she reported herself fairly well with occasional indigestion and loss of appetite; she had lost some weight, had occasional attacks of vertigo, but still did not appear to pick up strength.

On May 22, 1924, her blood count was—red blood-cells, 3,880,000; haemoglobin, 39 per cent.; white blood-cells, 6,800; colour index, 0·5; polymorphonuclears, 42·0; lymphocytes, 47·0; large mononuclears, 7·0; eosinophils, 2·0; basophils, 2·0; slight anisocytosis; platelets very abundant.

On March 20, 1927—red blood-cells, 4,000,000; white blood-cells, 8,500; haemoglobin, 50 per cent.; colour index, 0·62.

In March 1928 she reported herself fairly well, but had no appetite and her weight was 7 st. 7 lb.

She was seen by me for the first time on 18.3·30, when she complained of severe anaemia and jaundice which was becoming progressively worse, palpitation, dyspnoea, lassitude, loss of weight (now 6 st. 6 lb.), appetite, and strength, constipation, paraesthesiae of hands and feet, and some oedema of the feet at the end of the day.

Examination showed a considerable degree of anaemia with a marked yellow colour of the skin; artificial dentures; clean tongue; liver and spleen not enlarged; no alteration in reflexes, and nothing abnormal in the other systems.

X-ray examination (28.3.30) showed a very small stomach and a correctly working stoma at the site of the old gastro-enterostomy.

A fractional gastric analysis disclosed no free hydrochloric acid in the stomach.

The blood count was (18.3.30)—red blood-cells, 2,960,000; white blood-cells, 2,900; haemoglobin, 28 per cent.; colour index, 0·48.

She was treated with an active preparation of desiccated stomach (one ounce daily) and a mixture of hydrochloric acid and pepsin, and although the red blood-cells showed much improvement, there was little alteration in the haemoglobin. This treatment was then replaced (11.12.30) by pil. ferri, grains xlv, daily with marked improvement.

On 15.1.31 she complained of slight diarrhoea, some soreness of the tongue, and weakness. This improved again with the gradual increase in the haemoglobin and red blood-cell count.

On 16.7.31 the red blood-cells and haemoglobin reached their maxima of 4,460,000 and 78 per cent. respectively. She had put on weight and the palpitation, dyspnoea, appetite, &c., had improved very much. From that time onwards the red-cell count gradually fell with a less degree of reduction in the haemoglobin, so that the colour index showed a progressive increase

until on 25.2.32 the blood count was—red blood-cells, 2,730,000; haemoglobin, 66 per cent.; white blood-cells, 4,600; colour index, 1·2; aniso- and poikilocytosis marked, a few normoblasts and megaloblasts seen. She had had some indigestion, sore tongue, and palpitation. The blood picture was now typically one of pernicious anaemia, but in view of the reported results of some observers on iron therapy in pernicious anaemia the treatment with pil. ferri (grains cxx daily) was continued for two months without any improvement. On the 14.4.32 the blood count was red blood-cells, 2,600,000; white blood-cells, 6,500; haemoglobin, 66 per cent; colour index, 1·27; and she was given again one ounce daily of desiccated hog's stomach powder (Boots) without iron or acid. This time the response was very gratifying

TABLE VII

Case Showing Development of Microcytic Anaemia after Gastrectomy with Subsequent Alteration to a Macrocytic Anaemia (abridged table)

Date.	Red blood-cells $\times 10^6$.	Haemoglobin %.	Colour index.	White blood-cells.
22.5.25	3·88	39	0·5	6,800
20.3.27	4·00	50	0·62	8,500
18.3.30	2·96	28	0·48	2,900
18.6.30	3·05	23	0·38	4,200
16.7.30	4·38	21	0·23	—
11.12.30	4·11	32	0·39	5,400
15.1.31	4·06	46	0·57	—
26.3.31	4·11	66	0·8	4,600
23.4.31	4·27	60	0·71	6,200
21.5.31	4·19	60	0·7	4,600
16.7.31	4·46	78	0·88	4,600
21.9.31	3·75	58	0·78	5,800
4.11.31	3·65	56	0·77	3,600
14.1.32	3·25	52	0·81	5,400
25.2.32	2·73	66	1·2	4,600
3.3.32	2·92	72	1·24	6,200
31.3.32	2·70	64	1·19	5,100
14.4.32	2·62	66	1·27	6,500
5.5.32	4·50	75	0·8	5,400

so that after a further three weeks (Table VII) the blood count showed (5.5.32) red blood-cells, 4,500,000; haemoglobin, 76 per cent.; colour index, 0·8; and the patient felt so well that she discontinued her attendances at the clinic.

The case is of extreme interest, in as much as originally she had a severe hypochromic type of anaemia with low colour index following the gastric resection. This did not respond to the hog's stomach treatment as was to be expected, but marked improvement followed the exhibition of adequate iron therapy until the whole character of the anaemia changed completely; the patient had then an obvious pernicious anaemia, despite the adequate dosage of iron and, contrary to the results one might have anticipated from some clinician's results, she did not show improvement with iron therapy. On the other hand, substitution by an active desiccated stomach preparation ('Pepsac') now gave a rapid response as shown in Table VII. Thus, we see in the same patient the onset of two types of anaemias following hemigastrectomy—firstly a microcytic hypochromic anaemia, responding to iron,

but not stomach therapy, finally changing to a megalocytic hyperchromic anaemia responding to treatment with desiccated stomach, but not iron. This type of change has already been commented upon by Gram (62), Witts (199), and Vaughan (182).

TABLE VIII

Pernicious Anaemia Associated with Chronic Obstruction of Alimentary Tract

Author.	Reference.	No. of cases.	Diagnosis of stenosis.	Site of stenosis.
Barker and Hunter	5	1	Autopsy	Small intestine
Becker	8	1	Laparotomy	,,
Bretschneider	24	1	Autopsy	,,
Borchgrevink	17	1	,,	,,
Dubois	39	1	Laparotomy	Pylorus
Chapman and Duff	30	1	,,	Colon (stasis)
Faber Faber and Nyfeldt	47 48	1	Autopsy	Small intestine
Gluzinski	58	1	,,	,,
Haden	68	1	,,	Colon, duodenum
Hartmann, E.	73	1	,,	Small intestine (foreign body obstruction)
Holst	81	1	,,	Small intestine
Keefer	91	1	—	Intestine
Kretz	95	1	Autopsy	Caecum
Little, Zerfas, and Trusler	110	1	Laparotomy	Colon
Meulengracht	120	1	Autopsy	,,
Meulengracht	120	1	,,	Small intestine
Meulengracht	120	1	Laparotomy, radiologically	,,
Meulengracht	121	1	Radiologically	,,
Meulengracht	123	1	Radiologically, autopsy	,,
Schmidt, A.	158	2	Autopsy	,,
Schmidt, W.	159	1	,,	Descending colon
Seyderhelm	164	1	Laparotomy	Small intestine
Strandell	172	2	Autopsy	,,
Szczepanski	174	1	,,	,,
Wallis and Warfvinge	183	1	,,	,,
Wiechman and Zinsser	184	1	Radiologically	,,
Wilkinson	This series	1	,,	Colon (splenic flexure)
Zadek	203, 204	1	Autopsy	Transverse colon
Zadek	203, 204	1	,,	Small intestine

Chronic Intestinal Observation

The first case (1893) showing the occurrence of pernicious anaemia following chronic intestinal obstruction, due to either stenosis or foreign body, was reported by Faber (47), who also drew attention to the fact that severe anaemia was a frequent sequela of such intestinal stenoses, and that it might be frequently found in tuberculous children. He quoted a second case of Wallis and Warfvinge (183).

Since then a relatively small number of such cases has been reported from time to time (see Table VIII), and Meulengracht (123) in 1929 was able to collect and discuss a group of those that appeared to be examples of true

pernicious anaemia secondary to or following intestinal stenosis or obstruction by foreign body; he rejected two cases reported by Hale-White (69) and two others of Zadek's (203, 204) which only showed ulceration and scars without intestinal stenosis.

Castle quotes a case of Dubois (32), where an Addisonian type of anaemia occurred in a child of 13 years following pyloric obstruction by a mass of tuberculous glands—the case falls into this group, although not strictly intestinal; it has been considered above (p. 285). Other cases of pernicious anaemia associated with pyloric obstruction (malignant and non-malignant) have been described by Garvey and Stern (54), Israël (87), Ewing (46), Lazarus (105), Eisen (41), and also referred to by Labbé and Salomon (102). A further case in my own series here shows pernicious anaemia associated with chronic intestinal obstruction in the region of the splenic flexure of the colon.

A woman, aged 67 years, was admitted to hospital complaining of anaemia, weakness, lack of energy, shortness of breath on exertion, loss of appetite and weight, paraesthesiae in fingers and toes, some soreness of tongue occasionally, oedema of feet (ten months), and increasing constipation. For six months she had been having abdominal pains that were most severe on the left side—they had no relationship to meals, and she was often free for two or three days at a time. These symptoms had been getting worse for twelve months so that she had been in bed for the twelve weeks prior to admission. There was nothing of note in the previous medical and family histories. Examination showed a very pale, emaciated edentulous woman, weight 6 st. 2 lb.; blepharitis right side; superficial glossitis; onychogryphosis; varices in both legs. There was incontinence of urine and faeces. Lungs and heart normal. Abdominal wall was very thin and lax; there was irregular distension in the flanks and peristaltic waves were visible, while an indefinite mass could be felt in the left hypochondrium; spleen and liver not enlarged; knee-jerk and ankle-jerk reflexes present; plantar responses both extensor.

Blood count (18.10.32): red blood-cells, 1,640,000; haemoglobin, 39 per cent.; white blood-cells, 4,600; colour index, 1·2; aniso- and poikilocytosis; normoblasts and megaloblasts present. Fractional gastric analysis—achylia gastrica. Wassermann reaction negative.

Radiological examination (14.11.32) (Barium enema)—'The enema flowed to almost one inch proximal to the splenic flexure, but would not pass beyond this point, where there was also some irregularity. The appearances suggested neoplasm.'

She was given an active preparation of hog's stomach (188) and showed rapid response to treatment; the reticulocytes increased to 35·8 per cent. on the twelfth day, while the blood picture showed marked improvement. Clinically, the patient was very much better and was no longer incontinent.

On 7.12.32 the blood count was—red blood-cells, 2,800,000; haemoglobin, 62 per cent.; white blood-cells, 8,200; colour index, 1·09 and the patient was considered fit for a palliative caecostomy which was carried out on 28.11.32 by Mr. C. Roberts, F.R.C.S. The blood count on 22.12.32 was—red blood-cells, 3,600,000; haemoglobin, 64 per cent.; white blood-cells, 7,000; colour index, 0·89.

The diagnosis here depends upon the history, clinical examination, and radiological evidence, for although the anaemia was responding well to treatment, in spite of the possibility of malignancy she was unfit to permit of surgical manipulation, and it has only been possible to perform a palliative caecostomy in order to relieve the colonic obstruction.

Miscellaneous

The miscellaneous group calls for little comment. Two patients had parasitic infestation, namely, (i) round worm which was vomited on the second day of treatment, and (ii) thread worms. These were cured by the appropriate treatment. The occurrence of megalocytic anaemia of the Addisonian type is well known to be associated with intestinal worm infestation, such as dibothriocephalus latus, and ankylostoma duodenale, especially in Scandinavia and America, although they are of considerable rarity in this country. A voluminous literature has arisen in connexion therewith (13, 14, 153, 154, 156, 162, 175).

Three cases had diseases of the central nervous system other than postero-lateral-sclerosis of the spinal cord; these consisted of paralysis agitans, postencephalitis, and anterior poliomyelitis respectively.

One woman suffered from migraine, and one man has had recurrent alveolar abscesses for eighteen months. The blood pictures in all the cases in this group have remained within normal limits since the institution of treatment with hog's stomach from one to three years in all but one, the latter having only been under observation six months.

Conclusion

In a series of 370 cases of proved pernicious anaemia 23·2 per cent. also suffered from concomitant diseases.

It appears to be fairly conclusive from my own observations that in the absence of sepsis or infection the pernicious anaemia responds to treatment quite satisfactorily and in a normal manner independently of the second condition. On the other hand, the associated diseases also require their own specific treatments and do not improve unless these latter supplement the therapy administered for the Addisonian anaemia.

Thus it has been seen that when pernicious anaemia occurs in association with many other diseases each behaves independently as regards progress and response to treatment.

This does not apply, as has been indicated, when septic or infective conditions are present, for in such cases the response of the pernicious anaemia to treatment is seriously impaired and satisfactory therapy is dependent upon the removal of the complicating infection—as arises in cases with cystitis, pneumonia, &c. Acute conditions, like phthisis and neoplastic changes (where surgical treatment is impracticable) may progress to fatal terminations without markedly affecting the blood pictures, provided that

(i) the Addisonian anaemia is in the remittant stages at the time of onset of the secondary condition, and (ii) adequate treatment for the anaemia is maintained (188).

It is difficult to prove any definite common factor between pernicious anaemia and the various conditions occurring coincidently with it and discussed above.

The cardiovascular, urinary, pulmonary, and tuberculous conditions have apparently no obvious connexion, but it is commonly found that achlorhydria may occur in asthmatic, bronchitic, and tuberculous patients. On the other hand, I have already shown that some skin diseases (189, 196) very commonly associated with gastric dysfunction and certain gastro-intestinal symptoms (glossitis, flatulence, diarrhoea, &c.) are frequently found in cases of pernicious anaemia. In both conditions such symptoms may be entirely relieved by the same treatment.

Metabolic disturbances are also found in endocrine diseases, while achlorhydria is again a common finding, especially in diabetes mellitus, and hydrochloric acid may be as useful an adjunct as in pernicious anaemia. Anaemia with malignant disease, syphilis and following operation for gastro-intestinal ulceration have been discussed above, and again a frequent (but not invariable) common factor is the gastric secretory impairment.

It is not suggested that achlorhydria is responsible for the co-existence of pernicious anaemia and these diseases, rather is it a gastric condition common to many conditions. Thus, one must view the associations as quite fortuitous and accidental happenings in cases suffering from pernicious anaemia just as they may arise amongst normal people or patients suffering from any other diseases. It is obvious that, for example, such small tumours as have been found usually at autopsy (p. 294) can have little aetiological influence on the genesis of pernicious anaemia. The complicating diseases here discussed occur more frequently amongst people free from Addisonian anaemia, while seventy-seven per cent. of patients with pernicious anaemia do not show such complications.

Wm. Hunter (85) in discussing the occurrence of cancer with pernicious anaemia says:

'Hence I conclude, on general grounds alone, that when the two conditions—malignant disease and pernicious anaemia—are found associated, the connection is to be regarded, if not precisely as accidental, at least as not essential; that the malignant disease *per se* does not constitute the essential anatomical change underlying the pernicious anaemia associated with it, however much in certain situations it may at times be associated with effects resembling pernicious anaemia.'

This statement could be applied to nearly all the other complicating diseases discussed in this paper.

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THE COMPARATIVE VALUE OF DRUGS USED IN THE CONTINUOUS TREATMENT OF ANGINA PECTORIS[1]

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There is no agreement on the best routine treatment of angina pectoris by drugs. There has scarcely been a methodical attempt to compare the relative values of the many drugs that have been recommended, and uncontrolled and isolated observations have too often guided opinion. Certainly no particular remedy has achieved an outstanding reputation. Such haphazard knowledge alone would justify further investigation, but the present time is specially opportune as many of the older writings are valueless because of the confusion then existing between angina of effort and coronary thrombosis. Interest in the continuous treatment of angina of effort should now revive because an important source of fallacy in assessing its prognosis and the value of treatment has been removed by the separation of coronary thrombosis. The recognition of a better outlook in angina of effort is now becoming more general, so that any attempt to improve the continuous treatment should be worth while.

In the present investigation a systematic test was made of those medicinal remedies with any claim to be applied in the treatment of angina of effort. The direct comparative observations had the object of determining which drug is most beneficial in controlling the incidence and severity of recurring attacks. In this paper we shall deal exclusively with those therapeutic measures applied in continuous treatment. The immediate treatment of individual attacks has also been studied, but this will be discussed in a subsequent paper.

Selection of Patients and Scheme of Observation

The investigation has been carried out almost entirely on patients attending the Cardiac Department of the London Hospital, and the number of patients was steadily augmented with a view to this investigation. Angina pectoris is commoner among the present class of hospital patients than has been supposed. Our series consists of 90 patients, 73 males and 17 females; their ages ranged from 39 to 80 years, with an average of 59 years. Thirty were

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of the Jewish race. All patients belonged to the lower or lower middle classes, and all the females were engaged in household work. Twenty-nine patients were able to do their usual work throughout the investigation; 61 patients were unfit to work because of pain. This investigation has occupied two and a half years and the fatalities have been so few as to emphasize the scope for treatment in angina of effort. If the diagnosis of angina pectoris was in doubt after a careful history and physical examination the patient was excluded from the series. Eighteen with undoubted angina were rejected because they were considered unlikely to co-operate. The treatment of coronary thrombosis is not here considered, though reference will be made later to patients in whom it developed under observation. In forty cases there was a history of previous coronary thrombosis.

Patients with syphilitic angina pectoris were excluded, and in the present series all showed a negative Wassermann reaction. The blood-pressure was regarded as raised in thirty-one instances where the systolic pressure measured 160 mm. Hg. or higher and the diastolic pressure 100 mm. Hg. or higher. The highest figure recorded was 285/135, while in 10 cases it was 200/115 or over.

An *electrocardiogram* was taken as a routine. It showed left ventricular preponderance in 46, premature contractions in 4, partial heart block in one case, auricular fibrillation in 3 cases, right bundle branch block (old terminology) in 5, inversion of the T-wave in lead I in 11, in leads I and II in 4, and in leads II and III in 9 cases. Flattening of the T-wave in lead I occurred in 8, and in lead II in 5 cases. The QRS complex was slurred in 6 cases. *X-ray examination* of the heart and aorta was made in each case. There was enlargement of the heart to the left and the right in 16, and to the left and involving the left ventricle in 37 cases. Prominence of the aortic knuckle or a raised aortic arch was found in 12 cases. In the rest there appeared to be no obvious abnormality of the heart or aorta when examined radiologically. Aneurysm of the aorta was never seen.

If any investigation of the treatment of angina is to produce reliable results, the type of case selected for study should be clearly defined. Neglect of this essential has caused much confusion whenever the value of treatment has been in consideration. We shall therefore enumerate the criteria which qualified each patient for admission into the series as an undoubted case of angina pectoris. Thus, each patient had angina pectoris of effort characterized by recurrent attacks of substernal pain which spread across the chest and often passed through to the back; it frequently radiated to the shoulders, down one or both arms, and occasionally to the jaw and neck. The attack was always determined by physical exertion, and in many instances the act of eating or defaecating was sufficient to precipitate the pain. Emotion sometimes induced an attack in some of the cases, but only where physical movement would bring on the pain as readily. A few were subject to nocturnal attacks commonly excited by disturbing dreams. With

these exceptions attacks never occurred at rest. Pain was always relieved by rest, and quickly when the causative exercise was discontinued. The duration of the attack varied mostly with individual patients, and was one minute to one hour; in 71 patients the attacks lasted less than fifteen minutes.

The most difficult problem in devising a plan of observation on treatment was how to provide adequate control. With this object we adopted a scheme of treatment with placebo. Even then particular attention had to be paid to a number of factors which conspired to upset the value of control observations. Thus, it was always necessary to learn in every case the number of attacks produced by a known amount of exertion in a definite period, and the severity of these attacks and their duration when rest was taken, from their onset. Spontaneous variation in the severity of the pain, and occasionally the tendency to periods of relative freedom from attacks (remissions), had both to be considered. Gain or loss in body-weight, weather conditions, unusual emotional influences, and intercurrent illnesses, all had to be taken into account when assessing the value of the remedies tested, and appropriate notes were made on a specially printed form at each attendance. One of two placebos[2] was prescribed for a fortnight at the first attendance. Patients were instructed to make personal records of each attack, noting the nature of the exertion which had induced the pain, and the duration of the several attacks when rest was the only treatment accorded. Particulars of the frequency, severity, and duration of the anginal attacks prior to observation were also taken. Later, between trial periods of active drugs, control periods (placebo only) of two, four, or more weeks were introduced.

All patients were ambulatory; they visited the clinic at fortnightly or monthly intervals. Any untoward symptom due to the drug was noted. In order to avoid mental suggestion the drugs were prescribed in a mixture form whenever possible, and a simple colouring agent added where necessary. The following drugs were tested: sodium nitrite, mannitol hexanitrate, erythrol tetranitrate, potassium iodide, luminal, chloral, morphine, papaverine, phenacetin, diuretin, calcium diuretin, euphyllin, belladonna, digitalis, lacarnol, and harmol. Mannitol hexanitrate, erythrol tetranitrate, phenacetin, and calcium diuretin were prescribed in tablet form. Care was taken in arranging the order in which these drugs were prescribed so as to avoid giving two important drugs over consecutive periods, and an intervening period was often allotted during which the patient was given a placebo.

Much attention was directed to the reliability of the preparations used in the clinical trial. The question of standardization scarcely applied to these drugs except certain of the nitrite preparations. All are chemically pure

[2] R/. Sodium bicarbonate 15 gr. Infusion of gentian to ½ fluid oz.

R/. Liquor carmine ½ min. Sodium bicarbonate 15 gr. Infusion of gentian to ½ fluid oz.

substances of known stability and composition except belladonna, digitalis, euphyllin, and lacarnol. Belladonna and digitalis were both given as the B. P. (1914) tinctures. Euphyllin and lacarnol were administered as supplied through the dispensary.

In deciding the dosage of individual drugs the full effects were sought for, and often doses greater than usual were prescribed. Criticism of the short time accorded to the trial of each drug is met here by emphasizing three points. Continuous treatment with each drug for several consecutive test periods was invariably adopted in a certain number of patients. Further, the optimum dose was employed in each instance so that its maximum effects would appear well within the first week of the test period. Again, all drugs were prescribed an hour before food in order to ensure rapid absorption.

In order to illustrate the scheme on which this investigation was conducted the following account is given of one patient:

M. S., a male, aged 74 years, first attended the Cardiac Department in December 1930. He smoked and he drank in moderation. He was retired for many years and had suffered from angina for the past 2½ years. There was no history of coronary thrombosis. The pain over the middle third of the sternum spread across the chest and occasionally to the neck and down one or both arms as far as the wrists. It was induced by exertion, especially walking; when leaving his house in the morning it would compel him to stop after walking only a few yards. The attack usually lasted 5 minutes, but sometimes a bad attack lasted longer. He would then experience a 'second wind' for pain, and find that after relief from the first attack the next was not so readily induced. Depending on the amount of exercise taken he had two or three attacks each day. Nocturnal attacks were infrequent.

On examination. A man of short stature, cheerful disposition, and inclined to be stout. Weight, 12 st. 5 lb. Brachial, radial, and temporal arteries not unduly thickened for age. Slight displacement of the apex beat to the left suggested some enlargement of the heart. Aortic 2nd sound accentuated. B. P., 200/95. No evidence of syphilis. W. R., negative.

Electrocardiogram. Normal rhythm. Left ventricular preponderance. T-wave inverted in lead I, but upright and tall in leads II and III.

Radioscopy. Slight enlargement of the heart, and especially of the left ventricle; aorta, normal for age.

The patient was accepted as an undoubted case of angina of effort; he was judged to be co-operative and so was included in the series.

He was requested to keep a diary and to make particular reference to the following details at the end of each day: number of attacks, their severity and duration; nature of exercise inducing pain; distance walked each day and any form of exercise taken; weather conditions, with special reference to cold and wind.

On each subsequent visit the patient was taken into a private room and the interrogation usually lasted ten to fifteen minutes. The particulars which the patient had recorded daily in a note-book were entered on a specially printed form, and this ensured that no important item was overlooked at any visit. The results in this case are summarized, but particulars of a negative character, although noted, have not been recorded here.

Drug.	Duration of test (in days).	Total no. of attacks.	Severity of attacks.	Exercise and other variables.	Patient's impression of test period.
Placebo (gentian)	14	40	More severe	About ¼ mile daily	Worse
Placebo (gentian)	14	23	Less severe	5 minutes walk daily	Better
No medicine	14	23	—	Same	Better
Sodium luminal	14	42	1 very severe attack	10 minutes walk daily	Worse
Placebo (gentian and carmine)	14	18	—	Walking more, up to 1 hour daily	Better
Chloral	14	13	Less severe	One day he walked for 5 hours and only had one attack	Better
Diuretin	14	13	—	3 attacks accounted for by worry; his brother died suddenly. Walking 2 hours daily	Same
Morphine	14	9	Mild except for one bad attack	Walking 4 hours daily	Better. Constipation.
Potassium iodide	14	12	2 very bad attacks	Same	Same
Potassium iodide	28	16	5 very severe attacks	Patient on holiday; medicine for 3 weeks only; more walking, from 1 to 1½ miles daily	Worse
Phenacetin	14	15	Some of them very severe	At the most ½ mile each day	Much worse
Sodium nitrite	21	19	4 severe attacks. One lasted 1 hour	Walking ½ mile daily. Medicine only during first 14 days	No better
Papaverine	14	11	3 bad attacks; 1 at 4 a.m. lasting 1½ hours, while in bed	Same	Same
Euphyllin	14	9	All slight attacks	Same	Better
Belladonna	14	10	Mild attacks, but most of them at night	Same	Same
Mannitol hexanitrate	14	10	No severe attacks	Only took medicine for 2 days	Same. Giddiness soon after swallowing tablets
Placebo	21	8	2 bad attacks	Same	Same
Placebo	28	10	1 severe attack lasting 2 hours	Same	Slightly better

Drug.	Duration of test (in days).	Total no. of attacks.	Severity of attacks.	Exercise and other variables.	Patient's impression of test period.
Erythrol tetranitrate	21	16	7 attacks in first week when taking medicine	Confined indoors with 'influenza' last 14 days. No medicine during this time	Bad during first week
Sodium nitrite	14	9	Mild attacks	Same	Better. He states that he used to have terrible pain when the investigation started, but not now
Digitalis	14	6	Not severe	Same	Same
Placebo	14	12	Same	Weather mild and patient feels correspondingly better	Better
Sodium nitrite	14	56	Attacks stronger	Same exercise and no change in weather	Much worse
Lacarnol	14	42	Same	Same	No better. Vertigo and nausea after medicine
Euphyllin	14	42	1 bad day	Same	No better
Euphyllin	28	112	Some bad attacks	Same. Walking about ½ mile daily	Worse
Potassium iodide	28	About 100	Same	Same	Same
Placebo	28	84	Same	On holiday	Same
Placebo	28	96	Same	Same exercise	Same
Phenacetin	28	98	Same	Same	Same
Ca. diuretin	14	52	Occasional bad attacks	Walked just the same distance daily	No better

Results

The results obtained will be discussed under each drug prefaced by a summary of the literature. A further section will review the comparative effects of the drugs tested.

Control periods. (*Placebo.*) The value of remedies in relieving anginal pain cannot be judged unless the observations are properly controlled. The literature on the treatment of angina gives no indication that this side of the problem has been considered, although it is recognized that the disease pursues a varying course in regard to severity quite apart from any form of treatment. Gallavardin (25) pointed out that spontaneous remissions occur in about 8 per cent. of patients and sometimes last for years. His observations dealt with such long periods of remission that it is likely that

coronary thrombosis explained most of them. No facts seem to be available on variations in the severity of symptoms during the course of angina of effort over weeks or months. This knowledge is essential if we are to have control of therapeutic investigations. A contribution to this problem is furnished by our control observations.

Sixty-six patients were treated with a placebo for periods of four to twenty-six weeks. In some patients the periods of placebo treatment were consecutive, but usually they were separated by periods during which active drugs were taken. The results are discussed here in four different groups according to the frequency of anginal attacks during successive observation periods when compared with an initial test period of fourteen days. The four groups indicating different degrees of clinical response to treatment are defined as follows: (*a*) great improvement, indicating a decrease of more than 50 per cent. in the number of attacks; (*b*) moderate improvement, indicating a decrease of less than 50 per cent. in the number of attacks; (*c*) no improvement; (*d*) worse.

Of the 66 patients who received placebo treatment for more than one test period of fourteen days, 18 (27 per cent.) showed great improvement (*a*), which included complete relief from attacks for one or more observation periods. Seven (10·5 per cent.) showed moderate improvement (*b*), 22 (33·5 per cent.) showed no improvement (*c*), and 19 (29 per cent.) were worse (*d*).

In the first group (*a*), 12 out of the 18 patients had a reduction of 50 per cent. or more in attacks during more than one-half of the period of observation. The minimum period of observation of the cases in this group while taking a placebo was six weeks, the maximum period twenty-six weeks, and the average period 12·6 weeks. The minimum period of complete relief was two weeks, the maximum period fourteen weeks, and the average 5·1 weeks. In the second group (*b*), all 7 patients had moderate improvement for at least half the period of observation. The minimum period of observation in this group was four weeks, the maximum fourteen weeks, and the average 7·1 weeks. If the results in groups (*a*) and (*b*) are considered together they show that 25 (37·5 per cent.) out of the 66 patients had improvement ranging from slight reduction in attacks, up to complete freedom for one-half or more of the observation period.

The high figures indicating improvement in this series emphasize an earlier remark that most of the observations made on the continuous treatment of angina have been based on uncontrolled data.

Sodium nitrite. Sodium nitrite was applied in the treatment of angina pectoris by Matthew Hay (34) in 1883. He described in detail the great relief afforded to one patient by the drug in doses of 4 to 5 gr. (0·25 to 0·30 grm.) taken for several weeks, both during attacks and to prevent attacks. In this way his patient was able to undertake greater exertion without pain. Hay noted both the absence of disagreeable effects and tolerance. In the same year Collier (17) reported another patient who was given 3 to 5 gr. (0·2 to 0·3 grm.) of sodium nitrite three or four times daily,

and also about ten minutes before he undertook exercise which usually induced pain. The attacks were lessened in severity and duration, but were not abolished. Two years later, Simon (67) recorded a case in which the attacks ceased following the administration of sodium nitrite in 1 gr. (0·06 grm.) doses three times daily for an unnamed period. Gélineau (27) remarked on the excellent effects of sodium nitrite in all cases of angina pectoris in which he had tried it. In 1894 Sharp (66) reported the results of giving sodium nitrite in doses of 1 to 4 gr. (0·06 to 0·25 grm.) every three or four hours to 6 patients; they obtained great relief and later, when the usual pain returned, it again responded to the same treatment. He reported that nausea, vomiting, syncope, and headache were fairly common during its administration. Huchard (39) and Ringer and Murrell (60) had already drawn attention to the toxicity of sodium nitrite. Ringer and Murrell recorded the toxic symptoms occurring in 18 patients after a single administration of sodium nitrite in doses of 3 to 10 gr. (0·2 to 0·6 grm.); 4 out of 13 patients taking the smaller dose complained of eructations, nausea, and vomiting; 17 out of 18 were unable to continue taking the larger dose on account of vertigo, palpitation, headache, nausea, sweating, trembling, and cyanosis. In 1897 Ringer and Sainsbury (61) considered 1 gr. (0·06 grm.) three times daily to be an efficient dose, although larger doses were occasionally needed. They referred to one instance where the attacks ceased on 3 gr. (0·2 grm.), although trinitrin had failed to give relief. Gibson (28) mentioned 'alarming symptoms' when referring to sodium nitrite. Robinson (62) stated that although trinitrin and amyl nitrite were free from dangerous effects, this was not the case with sodium nitrite. On the other hand, a more convincing study made by Lublinski (46) showed that the dangerous effects described by Ringer and Murrell could not be substantiated except for doses outside the therapeutic range. Although this view has been confirmed by several observers, sodium nitrite does not seem to have gained in favour. Osler (55) in his lectures only gave it a passing reference, and Leech (44) remarked that sodium nitrite was not tolerated so well as trinitrin, but recommended it for the prevention of attacks. Apparently opinion on this point remained confused, for in 1916 Babcock (5) condemned the use of nitrites in this way without giving reasons.

Only the regular administration of sodium nitrite is considered here, and doses of 3 or 5 gr. (0·2 or 0·3 grm.) were given three times daily as a simple mixture to 42 patients, and the majority took the smaller dose. In 27 patients the duration of the test period was fourteen days, in 8 patients four weeks, in 2 patients six weeks, and in 5 patients ten to twenty-eight weeks.

Five (12 per cent.) patients were greatly improved (*a*), and 4 of these had complete relief from pain for at least one test period of fourteen days. Three (7 per cent.) patients were moderately improved (*b*). Twenty-one (50 per cent.) patients were not improved (*c*), and 13 (31 per cent.) were

definitely worse (*d*). In the last group 3 patients said that the drug caused palpitation and this induced pain. The results are given in Table I.

TABLE I

Summary of Results in 42 Patients Treated with Sodium Nitrite

	Average number of attacks in each patient during average test period.	Patients arranged in groups according to response to treatment.			
		Great improvement. (*a*)	Moderate improvement. (*b*)	No improvement. (*c*)	Worse. (*d*)
42 patients taking sodium nitrite	38	5	3	21	13
Same 42 patients taking placebo	30	12	5	11	14

Although 3 patients benefited greatly from the regular use of sodium nitrite, the total number (19 per cent.) who improved is much smaller than the corresponding number (40·5 per cent.) who improved when a simple placebo mixture was the only form of treatment. These results show that sodium nitrite is not effective in the continuous treatment of angina pectoris.

No serious complications occurred, and toxic effects were noticed in only 3 patients; 1 complained of throbbing in the head and 2 of giddiness. One of the latter patients had transient unconsciousness on one occasion ten minutes after taking 3 gr. (0·2 grm.).

Mannitol hexanitrate. Bradbury (9) introduced mannitol hexanitrate as a vasodilator in 1895. Little notice was taken of this work until Marshall and Wigner (49) examined the pharmacological properties of its derivative, mannitol pentanitrate. They showed that its vasodilator action began about half an hour after it had been taken by mouth, and lasted for three to eleven hours according to the dose. They found that mannitol pentanitrate was only half as active as erythrol tetranitrate, but much more active than mannitol hexanitrate, probably owing to greater solubility. The only advantages of mannitol hexanitrate over erythrol tetranitrate were its relative cheapness when prepared on a large scale and its greater stability. Since then mannitol nitrates have received only brief reference, and confusion between the two still exists. Mannitol hexanitrate is the only nitromannitol available commercially, and is the derivative always used when the drug is recommended. The pentanitrate has apparently never been tried, although shown by Marshall and Wigner to be far more active than the hexanitrate as a vasodilator.

Mannitol hexanitrate was prescribed in tablet form three times daily in doses of 2 gr. (0·12 grm.). It was tried in twenty-one cases of angina pectoris. In 3 patients the drug was given for periods of four to fourteen weeks, and in the remaining 18 patients for one test period of fourteen days.

Two (9·5 per cent.) patients were greatly improved (*a*) and had complete relief from pain for one test period, but the attacks returned in both during further test periods on the same drug. Only 1 (4·5 per cent.) patient showed moderate improvement (*b*), 13 (62 per cent.) patients were not improved (*c*), and 5 (24 per cent.) were definitely worse (*d*).

TABLE II

Summary of Results in 21 Patients Treated with Mannitol Hexanitrate

	Average number of attacks in each patient during average test period.	Patients arranged in groups according to response to treatment.			
		Great improvement. (*a*)	Moderate improvement. (*b*)	No improvement. (*c*)	Worse. (*d*)
21 patients taking mannitol hexanitrate	41	2	1	13	5
Same 21 patients taking placebo	32	6	2	9	4

In Table II these results are compared with those obtained during treatment by a placebo. They do not support the view that mannitol hexanitrate has claim to be used in the continuous treatment of angina.

The only toxic effects were giddiness in one case, indigestion in another, and headache with generalized body pain in a third.

Erythrol tetranitrate. Erythrol tetranitrate was first used in the treatment of angina by Bradbury (9, 10) in 1895. Although practically useless for particular attacks, it has retained a place in treatment because its vasodilator action is said to persist several hours, and so its regular administration has been advocated in order to reduce the number of attacks. Ferreira (23) noted its prolonged action and low toxicity. Greene (30) considered that it was valuable in controlling the attacks in patients with high blood-pressure. Brunton (14) stated that nitro-erythrol in doses of ½ gr. (0·03 grm.) three times daily would sometimes keep a patient with angina perfectly comfortable for years. No further investigation of its therapeutic action has been made, and, apart from passing recommendation, later writers have added nothing to our knowledge. Brooks (12) has recently stated that the best results are obtained from the almost constant use of erythrol tetranitrate or sodium nitrite, and Solis-Cohen and Githens (69) mention its use in doses of ½ gr. (0·03 grm.) every four hours for the prevention of attacks.

Erythrol tetranitrate was prescribed as tablets in doses of ½ gr. (0·03 grm.) three times daily. In 20 patients there was no improvement in any instance. In 13 (65 per cent.) the condition remained unchanged (*c*), and in 7 (35 per cent.) it was worse (*d*). In Table III these results are compared with those obtained from observations during control periods when the same patients received a placebo mixture. The results show that erythrol tetranitrate has no place in the continuous treatment of angina pectoris.

Headache and vomiting occurred in 1 patient soon after taking the drug, but no untoward effects were noticed in the remaining 19 patients.

TABLE III

Summary of Results in 20 Patients Treated with Erythrol Tetranitrate

	Average number of attacks in each patient during average test period.	Patients arranged in groups according to response to treatment.			
		Great improvement. (*a*)	Moderate improvement. (*b*)	No improvement. (*c*)	Worse. (*d*)
20 patients taking erythrol tetranitrate	89	0	0	13	7
Same 20 patients taking placebo	57	7	1	8	4

Potassium iodide. The administration of iodide in the treatment of syphilitic angina pectoris is universal practice, but in angina due to coronary atheroma its value is uncertain. Gée (26) who had previously demonstrated improvement in cases of asthma when treated with iodide, stated in 1883 that the cure of angina pectoris by this means was also possible. Guyot (33) referred to several cases in which the attacks had ceased for a long period following administration of sodium iodide. It is not clear whether syphilis was the aetiological factor in most of Guyot's cases which responded favourably to iodide. Huchard (37, 38) emphasized the necessity of prolonged treatment and recommended that 1 to 3 grm. (15 to 45 gr.) of potassium iodide should be given daily for one to three years. In 80 examples of true angina pectoris he reported 43 as completely cured, 22 as improved, and 15 who died. In those reported as cured there had been freedom from anginal attacks for periods of eighteen months or longer. In only 4 of these did Huchard append details of the history, and in 2 we notice that the age was 38 years; so that if these were true examples of angina pectoris it is not possible from his data to exclude syphilis as the cause. Brunton (13) in 1891 also recommended iodide, but again it is not possible to rule out syphilis in his cases.

In our series iodide was prescribed three times daily as a mixture containing 10 gr. (0·6 grm.) of potassium iodide. Forty-seven patients with angina pectoris were treated. In all of them syphilis had been excluded. In 9 patients potassium iodide was given for two weeks, in 26 for four weeks, in 4 for six weeks, in 2 for eight weeks, in 5 for twelve weeks, and in 1 for fourteen weeks. The results of this treatment are given in Table IV. Great improvement (*a*) occurred in 13 (27·5 per cent.) patients, moderate improvement (*b*) in 5 (10·5 per cent.), no improvement (*c*) in 20 (43 per cent.), and 9 (19 per cent.) patients were worse (*d*). Thus in 62 per cent. of patients under treatment with potassium iodide there was either no reduction or an actual increase in the number of attacks. These results show that

potassium iodide has little claim to use in the continuous treatment of non-syphilitic angina pectoris.

No complications or untoward symptoms were noticed in any of the patients during iodide administration.

TABLE IV

Summary of Results in 47 Patients Treated with Potassium Iodide

	Average number of attacks in each patient during average test period.	Patients arranged in groups according to response to treatment.			
		Great improvement. (*a*)	Moderate improvement. (*b*)	No improvement. (*c*)	Worse. (*d*)
47 patients taking potassium iodide	22	13	5	20	9
Same 47 patients taking placebo	26	15	5	15	12

Luminal. Sedative drugs have long been used in the treatment of angina. Gélineau (27) recommended potassium bromide for regular administration between the attacks, but Huchard (40) wrote that the efficacy of bromide was much exaggerated, and that in his hands it had not produced the excellent results described by others, although he advised it when a considerable neurotic element was added to the clinical picture. In the same paper he also discounted the use of sulphonal, urethane, and ethyl carbamate because their action was too slow and their after-effects, drowsiness, &c., were too pronounced. Martinet (51) also held that bromide was particularly valuable in the presence of added neurosis, and Mackenzie (48) and Kohn (42) both supported this view. There is no detailed study in the literature of the effects of sedatives, so we have included both luminal and chloral in the present investigation. Luminal is a powerful member of the group; it has a rapid and certain action, and toxic effects are rare. Only passing reference ever seems to have been made to its use in angina. Luminal, in combination with theobromine (theominal), has recently been advocated for the prevention of attacks by a number of writers, especially by Romberg (63). It was decided not to investigate the effects of theominal because both its active constituents, luminal and theobromine, were investigated separately, the latter as diuretin.

In our series 59 patients received 1 gr. (0·06 grm.) of sodium luminal, three times daily, for a period of fourteen days. In 5 patients it was continued for one month, in 1 patient for six weeks, and in another for eight weeks. The results of this treatment compared with those for a placebo are shown in Table V. Eight (13·5 per cent.) patients showed great improvement (*a*) on luminal, whereas 17 (28·5 per cent.) showed great improvement (*a*) while taking a placebo. Only 1 (1·5 per cent.) patient obtained complete relief for at least one period of a fortnight, although 17 (28·5 per cent.) showed this degree of relief while taking a placebo. Fourteen (24 per cent.)

patients showed moderate improvement (*b*), 30 (50·5 per cent.) no improvement (*c*), and 7 (12 per cent.) were worse (*d*) while taking luminal. Thus we can adduce no evidence that luminal is of value in continuous treatment.

Nine (15 per cent.) patients complained of minor toxic symptoms due to the drug; slight drowsiness occurred in 6, slight drowsiness and vertigo in 3, and vertigo with slight mental confusion in 3. No other abnormal effects were seen, and we think that unwarranted prominence has been given to rashes (16, 52), gastro-intestinal disturbance with severe diarrhoea and mental hebetude or delirium (15, 19), as common toxic symptoms. They are all rarer than drowsiness and vertigo with slight mental confusion.

TABLE V

Summary of Results in 59 Patients Treated with Luminal

	Average number of attacks in each patient during average test period.	Patients arranged in groups according to response to treatment.			
		Great improvement. (*a*)	Moderate improvement. (*b*)	No improvement. (*c*)	Worse. (*d*)
59 patients taking luminal	22	8	14	30	7
Same 59 patients taking placebo	29	17	7	21	14

Chloral. Neither Liebreich (45) nor Bouchut (8), who introduced chloral as a hypnotic, mentioned its use in angina pectoris. It was Strange (71) who suggested that it might be so used and as a substitute for opium. He described two patients in whom its continuous use as a nightly hypnotic in a dose of 25 gr. (1·5 grm.) greatly relieved the nocturnal attacks. One of these patients took the drug every night for four months without ill effects. Walshe (72) in 1873 mentions 'a case having all the attributes of true angina' in which the attacks were frequent, but ceased under the influence of chloral (10 gr. or 0·6 grm.) taken twice daily. In 1877 Gairdner (24), in his classical article on angina pectoris, referred to only one case in which he had used chloral; here exceptional freedom from nocturnal attacks after an accidental overdose of 180 gr. (12 grm.) led to its continued use in doses of from 30 to 60 gr. (2 to 4 grm.) daily with marked improvement and eventually freedom from pain, although the patient had returned to work. Huchard (40) included chloral in a review of useless and dangerous remedies in angina on the grounds of its depressant effects on the heart muscle. Since then the use of chloral in angina has been alternately praised and condemned when not ignored. Gibson (28) regarded the drug as 'of comparatively little importance in the treatment of serious cardiac pain'. Barié (6) held that chloral had a place in treatment, although it was inferior to morphine. Osler (55, 56) did not mention chloral either in his 'Lectures on Angina Pectoris' in 1897, or in his Lumleian lectures in 1910. Similarly, Brunton (14) did not consider chloral worthy of comment.

Mackenzie (48) strongly advocated the use of chloral in angina and preferred it to any preparation of opium because it was less liable to produce mental or digestive disturbances. He recommended that its administration should be pushed in severe cases to obtain relief. Pal (57) recorded relief from attacks for two days in one patient after subcutaneous injection of 1 c.c. of a 50 per cent. solution along with 120 gr. (8 grm.) administered by mouth. Thus chloral seems to have proved valuable in the treatment of frequently recurring attacks of angina.

Reluctance to give chloral a satisfactory clinical trial seems to be due to misunderstanding of its pharmacology. The prominence given to its dangers is based largely upon analogy with the established effects of the drug when given to experimental animals in excessive doses. This is not supported by observations upon the effects of therapeutic doses in patients. Martinet (50) and Glaus (31) have shown that its action is satisfactory and safe, especially for securing sleep in cardiac failure or high blood-pressure. In our series of patients no serious untoward effects have followed administration of the drug in doses of 30 gr. (2 grm.) daily for periods of a fortnight up to $3\frac{1}{2}$ months.

It was prescribed in doses of 10 gr. (0·6 grm.) three times daily as 1 drachm of syrupus chloral (B. P. 1914). It was tried in 56 patients. The usual period of administration was fourteen days, but in 10 patients treatment was continued for periods varying from four to fourteen weeks. The results are given in Table VI.

TABLE VI

Summary of Results in 56 Patients Treated with Chloral

	Average number of attacks in each patient during average test period.	Patients arranged in groups according to response to treatment.			
		Great improvement. (*a*)	Moderate improvement. (*b*)	No improvement. (*c*)	Worse. (*d*)
56 patients taking chloral	19	19	13	15	9
Same 56 patients taking placebo	30	17	4	20	15

Nineteen (34 per cent.) patients showed great improvement (*a*) on chloral and 6 (11 per cent.) of these had complete relief for at least one fortnightly period; as many as 17 (30 per cent.) had this temporary complete relief during periods on a placebo only. Thirteen (23 per cent.) patients showed moderate improvement (*b*), 15 (27 per cent.) no improvement (*c*), and 9 (16 per cent.) were worse (*d*) when taking chloral.

Apart from a greater incidence of moderate improvement (*b*) in patients on chloral, these results of treatment with chloral and placebo are almost identical. They show that chloral has a slight effect in reducing the frequency of attacks in a small proportion of patients, but in our opinion this

degree of improvement has not been sufficient to justify its routine use in continuous treatment. Minor toxic symptoms attributable to chloral were met with in 6 patients; drowsiness and depression occurred in 4, vertigo in 1, and a sensation of heat over the face in another. No rashes or dyspeptic symptoms were reported.

Morphine. Opium has been used for the treatment of angina pectoris ever since Heberden (36) first described the disease in 1768. He observed the relief afforded in attacks and recommended its use for the prevention of nocturnal attacks. In 1799 Parry (58) suggested the regular use of opium with the object of reducing the frequency of attacks. Although Parry's suggestion received little comment and no trial, opium became established as one of the best remedies for relieving anginal attacks. Latham (43), in his lectures in 1846, remarked that in repeated attacks 'any other remedy is utterly useless but opium', a dictum which remained unchallenged until the introduction of the nitrites.

We are only concerned here with the effects of opium and morphine in reducing the frequency of attacks when given continuously as first suggested by Parry. Gélineau (27) in 1887 warned against the routine use of the drug in angina in case it should lead to morphine addiction. He gave no records of personal observation to support this view. Schott (65) regarded morphine as the best drug to reduce the number of attacks in angina, but spoke of injurious effects on the heart when given for prolonged periods. Neither Gairdner (24) nor Osler (55) in their monographs on angina mentioned the use of opium or its derivatives in continuous treatment. Schneider (64) in 1930 reported on the continuous use of the morphine derivative, dilaudid, in angina pectoris. He gave doses of 0·001 grm. (1/60 gr.) twice or three times daily by the mouth until the attacks ceased, but if necessary he continued the treatment for several months. Thirty patients were treated in this way and, although no detailed reference is made to the relief obtained, the attacks often abated within ten to twenty days. He mentions benefit from rest in bed at the beginning of treatment, but makes no comment upon the fallacy which this introduces into his results.

We selected morphine and papaverine for study in the present investigation because they are the most typical representatives of the two groups of opium alkaloids. Dilaudid, dicodid, eukodal, and other synthetic derivatives which have recently been introduced, do not essentially differ from morphine.

Forty-eight patients were treated with morphine for periods varying from two to twelve weeks. It was prescribed as liquor morphini hydrochloricus (B. P. 1914) in doses of 15 minims (1 mils.) (containing 1/8 gr. or 0·008 grm.) three times daily. In addition 4 patients were given twice this dose for periods varying from two to four weeks. An analysis of the results obtained is given in Table VII.

Sixteen (33·5 per cent.) patients were greatly improved (*a*) and 2 of these were completely free from attacks for one fortnightly period. When

the same 48 patients were given placebo treatment, 15 (31·5 per cent.) were greatly improved (*a*) and all of these had complete relief for at least one fortnightly period. These results suggest that morphine has little value in continuous treatment. On the other hand 11 (23 per cent.) showed moderate improvement (*b*) on morphine compared with only 3 (6 per cent.) on placebo. Fifteen (31·5 per cent.) showed no improvement (*c*), and 6 (12 per cent.) were worse (*d*), while taking morphine compared with 16 (33·5 per cent.) who showed no improvement (*c*), and 14 (29 per cent.) who were worse (*d*), while taking a placebo. The average number of attacks for each patient per fortnight was twenty-one during morphine and thirty-two during placebo administration. Morphine, therefore, when given continuously has some slight effect in reducing the frequency of attacks. This improvement is so limited, however, that it can only have a minor value in continuous treatment. Those patients who took the larger dose of morphine failed to show any greater improvement.

Constipation was the only common untoward symptom and appeared in 25 per cent. of the patients. Vertigo and insomnia occurred in one case, and vertigo and nausea in another.

TABLE VII.

Summary of Results in 48 Patients Treated with Morphine

	Average number of attacks in each patient during average test period.	Patients arranged in groups according to response to treatment.			
		Great improvement. (*a*)	Moderate improvement. (*b*)	No improvement. (*c*)	Worse. (*d*)
48 patients taking morphine	21	16	11	15	6
Same 48 patients taking placebo	32	15	3	16	14

Papaverine. Individual writers have from time to time advocated the use of papaverine in conditions associated with spasm of smooth muscle. Pal (57) referred to its use in angina pectoris whereby severe attacks were relieved by intravenous injections of 0·01 grm. (1/6 gr.) of the hydrochloride, though in repeated attacks the effect was not lasting, except in one patient. Boehm (7) used a combination of cadechol, a camphor derivative, with papaverine, and stated that the attacks often disappeared entirely. Kohn (42) used papaverine in doses of 0·04 grm. (3/5 gr.), three times daily, for patients who failed to respond to treatment by drugs of the caffeine group.

In our series 31 patients were treated with papaverine. The hydrochloride was administered as a simple solution by mouth in doses of 1/8 gr. (0·008 grm.) three times daily for one or more test periods of fourteen days. The results are shown in Table VIII.

Nine (29 per cent.) patients were greatly improved (*a*), and 2 of these

had complete relief for at least one test period of fourteen days. When the same 31 patients were given a placebo, 9 (29 per cent.) were greatly improved, (*a*) and all were completely free from pain for at least one test period. Seven (22·5 per cent.) patients showed moderate improvement (*b*), 8 (26 per cent.) no improvement (*c*), and 7 (22·5 per cent.) were worse (*d*) on papaverine, whereas 3 (10 per cent.) showed moderate improvement, 11 (35 per cent.) no improvement, and 8 (26 per cent.) were worse on a placebo.

TABLE VIII

Summary of Results in 31 Patients Treated with Papaverine

	Average number of attacks in each patient during average test period.	Patients arranged in groups according to response to treatment.			
		Great improvement. (*a*)	Moderate improvement. (*b*)	No improvement. (*c*)	Worse. (*d*)
31 patients taking papaverine	27	9	7	8	7
Same 31 patients taking placebo	29	9	3	11	8

Thus a greater number of patients showed moderate improvement with papaverine when compared with a placebo, although this was less than with morphine. The difference, however, is slight and does not support the view that papaverine has any real value in continuous treatment. A comparison of the results obtained from the administration of morphine and papaverine shows that they differ in no important particular except that morphine is much more likely to produce constipation, which occurred in only one patient during treatment with papaverine. No other toxic effects were observed.

Phenacetin. The coal-tar analgesics were used in the treatment of angina shortly after their introduction into therapeutics in 1884. Arduizy (40), a pupil of Huchard, published his thesis in 1885 claiming good results from the use of antipyrin, and two years later this was supported by Ignatoff (40) in another thesis. In the same year, however, Huchard (38) pointed out the danger of collapse attending the use of this drug and considered that it should be excluded on account of this risk, together with other members of the same group. Writing again in 1892, Huchard (39) included antipyrin in a review of useless and dangerous drugs in the treatment of angina. Among those who have since opposed its use are Barié (6) and Schott (65). Since this time we have found no reference to the use of antipyrin in the treatment of angina. Phenacetin also seems to have received no mention.

We selected phenacetin as a typical member of the coal-tar analgesics because it is in common use and almost entirely free from risk of the serious collapse which has often been reported with antipyrin, and it can be given with safety in full therapeutic doses. Twenty patients were given 10 gr.

(0·6 grm.) of phenacetin in tablet form three times daily. In 17 cases it was continued for fourteen days, in 2 cases for four weeks, and in 1 case for six weeks.

The results are shown in Table IX. Six (30 per cent.) patients obtained great improvement (*a*) and one of these had complete freedom for one fortnightly test period. On the other hand 7 (35 per cent.) obtained great improvement while taking a placebo, and all of these had complete relief for at least one fortnightly period. Four (20 per cent.) patients showed moderate improvement (*b*), 6 (30 per cent.) no improvement (*c*), and 4 (20 per cent.) were worse (*d*), during phenacetin administration. The Table shows that treatment with phenacetin did not provide significant improvement. No toxic effects were noted.

TABLE IX

Summary of Results in 20 Patients Treated with Phenacetin

	Average number of attacks in each patient during average test period.	Patients arranged in groups according to response to treatment.			
		Great improvement. (*a*)	Moderate improvement. (*b*)	No improvement. (*c*)	Worse. (*d*)
20 patients taking phenacetin	33	6	4	6	4
Same 20 patients taking placebo	26	7	1	6	6

Diuretin (*Theobromine-sodio-salicylate*). Askanazy (3) in 1895 was the first to report benefit from diuretin in cardiac asthma with or without angina pectoris. He held that it relieved anginal attacks by dilating certain vessel-areas and not because of analgesia due to the salicylic radicle. In 1902 Breuer (11) also reported so favourably upon diuretin in cardiac asthma and angina that he held it to be the finest therapeutic triumph of the preceding ten years. Although the drug was absorbed too slowly for the relief of attacks, he often found that they ceased for a few days after theobromine treatment. He used 3·5 grm. (53 gr.) as the total daily dose. In 1925 Kaiser (41) reported no improvement in his own case from taking iodine and diuretin, transient improvement from intravenous injections of brom-calcium, but great though temporary improvement from calcium-diuretin, when taken in doses up to 3 grm. (45 gr.) daily for fourteen days with intervals of eight weeks. In 1925 Askanazy (4) wrote of his sixteen years' experience of diuretin in the treatment of cardiac asthma and angina pectoris, but only in general terms. Willius (74) preferred theobromine itself, and found great improvement in one-third of his cases observed for two years. Reitmann (59) observed in himself that diuretin in effective doses produced nausea and indigestion, but that 3 grm. (45 gr.) of calcium diuretin daily reduced the incidence of attacks. Gilbert and Kerr (29) made a valuable study of cases

of angina pectoris treated with purine-base diuretics. In 14 cases treated with theobromine there was no relief in 4, slight in 1, moderate in 6, and marked relief in 3. In 69 patients treated with diuretin they found no relief in 20, slight in 1, moderate in 10, and marked relief in 38. No control periods are recorded.

In our series diuretin was tested in 53 patients. Forty-one took 15 gr. (1 grm.) three times daily as a simple mixture. The remaining 12 took 15 gr. (1 grm.) of calcium diuretin in tablet form three times daily. A trial period of fourteen days was made in 37, four weeks in 9, six weeks in 4, and for periods varying from eight to twenty weeks in 3 patients.

TABLE X

Summary of Results in 53 Patients Treated with Diuretin

	Average number of attacks in each patient during average test period.	Patients arranged in groups according to response to treatment.			
		Great improvement. (*a*)	Moderate improvement. (*b*)	No improvement. (*c*)	Worse. (*d*)
53 patients taking diuretin	24	10	5	30	8
Same 53 patients taking placebo	27	17	5	18	13

Ten (19 per cent.) patients showed great improvement (*a*); 6 of these had complete relief for at least one test period of fourteen days, but 4 had similar relief on placebo treatment, and the attacks returned in another patient during a further trial period on diuretin. Five (9·5 per cent.) patients showed moderate improvement (*b*), 30 (56·5 per cent.) no improvement (*c*), and 8 (15 per cent.) were worse (*d*). One patient maintained that each dose of diuretin induced an anginal attack. These results have been summarized in Table X, and are compared with those obtained from control periods during which a placebo was the only treatment given.

This comparison shows that diuretin has no value in the continuous treatment of angina pectoris. There seems to be little or no difference between the value of diuretin and calcium diuretin. In twelve patients treated with calcium diuretin, 1 showed great improvement, 4 moderate improvement, 5 no improvement, and 2 were worse.

Slight toxic symptoms in the form of anorexia and nausea were noted but once.

Euphyllin (*Theophylline-ethylene-diamine*). Euphyllin, mentioned by Dessauer (20) in 1908, is a combination of theophylline (78 per cent.) and ethylene-diamine (22 per cent.). All xanthine derivatives dilate the coronary arteries in experimental animals, but according to Smith, Miller, and Graber (68) euphyllin is the most powerful. They found that it increased the rate of perfusion in the intact heart from 40 per cent. to 90 per cent. independently of any cardiac acceleration. These observations

confirmed the earlier experiments of Heathcote (35) with theophylline. Musser (53) described benefit from euphyllin in 7 cases of angina pectoris. Gilbert and Kerr (29) investigated its effects in 43 cases and found marked relief in 28, moderate in 3, slight in 3, and none in 9 cases. White, in his recent book (73), states that euphyllin in doses of 1½ to 3 gr. (0·1 to 0·2 grm.), three times daily, appears to be more effective than other purine derivatives and about half the cases of angina pectoris improve during its administration.

Euphyllin was prescribed by us in doses from 3 to 5 gr. (0·2 to 0·3 grm.) three times daily in a simple mixture for periods of fourteen days or longer in 37 patients. Twenty-nine took the lesser dose and 8 the larger dose. Seventeen took euphyllin for one test period of fourteen days, 9 for four weeks, 6 for six weeks, 2 for ten weeks, and 3 for periods of twelve, fourteen, and sixteen weeks respectively. The results are given in Table XI.

TABLE XI

Summary of Results in 37 Patients Treated with Euphyllin

	Average number of attacks in each patient during average test period.	Patients arranged in groups according to response to treatment.			
		Great improvement. (*a*)	Moderate improvement. (*b*)	No improvement. (*c*)	Worse. (*d*)
37 patients taking euphyllin	36	7	3	16	11
Same 37 patients taking placebo	31	12	3	12	10

Seven (19·5 per cent.) patients were greatly improved (*a*) on the smaller dose, and 5 of these had complete relief from attacks for one test period of fourteen days, but the pain returned during further treatment with the drug. Three (8 per cent.) patients showed moderate improvement (*b*), 16 (43 per cent.) no improvement (*c*), and 11 (29·5 per cent.) were worse (*d*).

These results do not show any advantage in favour of euphyllin when they are compared with the results of placebo treatment.

Nausea and vomiting were attributed to the drug by one patient taking 9 gr. (0·56 grm.) daily. No untoward symptoms were met in the remaining 36 patients, although 8 were taking 15 gr. (1 grm.) daily.

Belladonna. Reference to the use of atropine or belladonna in the treatment of angina pectoris is scanty. Allbutt (1) referring to digitalis therapy in angina, recommended its use only in combination with atropine. Later he (2) advocated the systematic use of atropine in continuous treatment in order to ward off vagal arrest, which he maintained followed the shock of the pain and was the immediate cause of death. Stevens (70), however, reported no benefit from its continuous use.

Twenty minims (1·2 mils.) (1/150 gr. or 0·0004 grm. of alkaloid) of the tincture of belladonna (B.P. 1914) were prescribed three times daily in

15 patients. It was continued for one test period of fourteen days in 10, for four weeks in 4 patients, and for eight weeks in 1 patient.

One (6·5 per cent.) patient showed great improvement (*a*) and remained free from attacks for a period of eight weeks. Moderate improvement (*b*) occurred in 1 (6·5 per cent.) patient, no improvement (*c*) in 7 (47 per cent.), and 6 (40 per cent.) patients were worse (*d*). The results are summarized in Table XII, where they are compared with those of placebo treatment. They do not suggest that belladonna has any value in the continuous treatment of angina pectoris.

No toxic symptoms were met with in any of the patients.

TABLE XII

Summary of Results in 15 Patients Treated with Belladonna

	Average number of attacks in each patient during average test period.	Patients arranged in groups according to response to treatment.			
		Great improvement. (*a*)	Moderate improvement. (*b*)	No improvement. (*c*)	Worse. (*d*)
15 patients taking belladonna	48	1	1	7	6
Same 15 patients taking placebo	35	4	2	5	4

Digitalis. Although digitalis therapy in angina pectoris has had supporters, there have been as many who have condemned its use, maintaining that it commonly renders the attacks more severe and frequent. Yeo (75) mentioned that 5 minims (0·3 mils.) of the tincture of digitalis three times daily might produce long periods of immunity from attacks. Allbutt (1) held that digitalis should not be used for angina unless combined with atropine. Even in cases where angina was associated with heart failure, digitalis appeared to produce harmful results. Danielopolu (18) wrote that contrary to current opinion he had used digitalis in 18 cases with satisfactory results. Brooks (12), however, agreed with earlier opinions that digitalis often increased the severity and frequency of the attacks. Fenn and Gilbert (22), from a combined experimental investigation of the intact heart in 13 dogs and observations on 7 patients, concluded that digitalis may induce angina by constricting the coronary arteries. Objection to the use of digitalis in clinical doses because it raised the blood-pressure is no longer tenable (47).

Twenty minims (1·2 mils.) of the tincture of digitalis (B.P. 1914) were prescribed three times daily to 19 patients. Auricular fibrillation was present in 3, and in 2 of these symptoms and signs of heart failure were prominent. The drug was administered to 15 patients for a test period of fourteen days, to 1 for three weeks, to 1 for four weeks, to 1 for six weeks, and to another for twenty weeks. Great improvement (*a*) occurred in 3 (16 per cent.) patients, moderate improvement (*b*) in 1 (5 per cent.), no

improvement (*c*) in 8 (42 per cent.), while 7 (37 per cent) were worse (*d*). These results are given in Table XIII.

TABLE XIII

Summary of Results in 19 Patients Treated with Digitalis

	Average number of attacks in each patient during average test period.	Patients arranged in groups according to response to treatment.			
		Great improvement. (*a*)	Moderate improvement. (*b*)	No improvement. (*c*)	Worse. (*d*)
19 patients taking digitalis	34	3	1	8	7
Same 19 patients taking placebo	25	4	2	7	6

In 2 of the 3 patients where auricular fibrillation was established, amelioration of the failure symptoms occurred during digitalis administration along with moderate reduction in the frequency of the attacks in one and great reduction in the other. The third patient, where auricular fibrillation was present without failure symptoms, became worse while taking digitalis and died at his home from what appeared to be coronary thrombosis; there was no necropsy.

The impression we have gained is that digitalis is useful only in treating those uncommon cases of angina pectoris where auricular fibrillation is present and where symptoms of heart failure have developed. Even then the symptoms of failure are more benefited than the attacks.

One patient complained of giddiness, nausea, and palpitation, but no others complained.

Lacarnol. Lacarnol, an extract 'prepared from mammalian tissues', is said to contain a cardiac hormone which dilates the coronary vessels, and to be of use in the treatment of angina pectoris. Fahrenkamp (21) has treated over 150 cases of angina by oral administration of 30 to 60 drops of lacarnol daily. Although he extols its merits he adds, 'lacarnol has much less effect on patients with marked coronary sclerosis as compared with its action on those angio-pathological conditions which have an angio-spastic basis, and it is important to bear this in mind when selecting cases for lacarnol therapy.' Neilsen (54) treated 18 patients with lacarnol; 12 of these derived so much benefit that they remained completely free from attacks for an observation period in no case less than three months. There was no attempt to establish control observations.

In our series lacarnol was tried in 15 patients. It was prescribed in doses of 25 minims (1·6 mils.) by mouth three times daily as recommended by the manufacturers. In 10 patients treatment was continued for one test period of fourteen days, and in 5 patients for four weeks.

Two (13 per cent.) patients showed great improvement (*a*) and remained free from attacks during one test period of fourteen days, but in both patients

the attacks returned during a further test period on lacarnol. One (7 per cent.) patient showed moderate improvement (*b*), 6 (40 per cent.) no improvement (*c*), and 6 (40 per cent.) were worse (*d*).

Since this we have observed many patients who have taken lacarnol for months without intermission, but in no instance with convincing evidence of improvement from its use.

One patient experienced nausea, vomiting, and giddiness about five minutes after taking each dose. Two patients were convinced that lacarnol induced anginal attacks. Coronary thrombosis occurred in 2 patients during the lacarnol test period.

Harmol. Gunn and MacKeith (32) have shown that harmol is a powerful dilator of the coronary vessels in animals. A solution of 1 in 200,000 produced an increase of 40 per cent. in the flow through the isolated heart of a rabbit. They concluded that this dilatory action was quantitatively selective, and that their findings indicated trial of harmol in patients with angina pectoris. At the request of the Therapeutic Trials Committee of the Medical Research Council, one of us (W. E.) investigated the effect of two harmol derivatives in the treatment of angina pectoris. Both these substances were supplied by Messrs. Boots Pure Drug Co. Ltd. Harmol hydrochloride was tested in 25 patients, in 2 of whom syphilis was the cause. Moderate improvement occurred in 6, no improvement in 9, and 10 patients were worse. Similarly in 7 cases treated with 0-n-propylharmol lactate, 5 showed no improvement and 2 were worse. These results seem to indicate that harmol, when administered by mouth in its present form in the continuous treatment of angina, is not efficacious in lessening the number and severity of attacks.

Discussion

The continuous treatment of angina of effort still remains unorganized, and the many drugs in common use have been alternately praised or condemned, so that there is no agreement upon the best drug to give. Two factors appear to have contributed to this lack of precision.

In the first place, the earlier literature on the subject is confused by the inclusion of coronary thrombosis. It is almost certain that the definite views held and applied in treatment as far back as 1846 can be so explained. Latham (43), for instance, stated that in repeated attacks of angina 'any other remedy is useless but opium'. It is likely that coronary thrombosis was present in most of his patients. The separation of this condition has given to angina of effort a much better prognosis. Thus, of our 90 patients with angina of effort only 13 developed coronary thrombosis while under observation, and only 5 of these died. Further, angina had been present for over two years in 40 patients in our series when first seen, and for over four years in 19 patients. These facts suggest great scope for continuous treatment.

The second factor which has hindered progress in treatment has been disregard of the natural variations or, even remissions, which occur in the course of the disease. We believe that this explains why most remedies have appeared to produce good results on occasion. It has been known that remissions occur, but we have not found in the literature any exact statement as to their frequency and duration when assessing the apparent good

TABLE XIV

Summarizing the Effects of Thirteen Drugs in the Continuous Treatment of Angina Pectoris Compared with the Effects of Control Treatment with Placebo

Drug.	No. of patients.	Patients arranged in groups according to response to treatment.				Average no. of attacks in each patient during average test period.
		Great improvement. (*a*)	Moderate improvement. (*b*)	No improvement. (*c*)	Worse (*d*)	
Placebo	*66*	*18*	*7*	*22*	*19*	*29*
Sodium nitrite	42	**5**	**3**	**21**	**13**	**38**
Placebo		*12*	*5*	*11*	*14*	*30*
Mannitol hexanitrate	21	**2**	**1**	**13**	**5**	**41**
Placebo		*6*	*2*	*9*	*4*	*32*
Erythrol tetranitrate	20	**0**	**0**	**13**	**7**	**89**
Placebo		*7*	*1*	*8*	*4*	*57*
Potassium iodide	47	**13**	**5**	**20**	**9**	**22**
Placebo		*15*	*5*	*15*	*12*	*26*
Luminal	59	**8**	**14**	**30**	**7**	**22**
Placebo		*17*	*7*	*21*	*14*	*29*
Chloral	56	**19**	**13**	**15**	**9**	**19**
Placebo		*17*	*4*	*20*	*15*	*30*
Morphine	48	**16**	**11**	**15**	**6**	**21**
Placebo		*15*	*3*	*16*	*14*	*32*
Papaverine	31	**9**	**7**	**8**	**7**	**27**
Placebo		*9*	*3*	*11*	*8*	*29*
Phenacetin	20	**6**	**4**	**6**	**4**	**33**
Placebo		*7*	*1*	*6*	*6*	*26*
Diuretin	53	**10**	**5**	**30**	**8**	**24**
Placebo		*17*	*5*	*18*	*13*	*27*
Euphyllin	37	**7**	**3**	**16**	**11**	**36**
Placebo		*12*	*3*	*12*	*10*	*31*
Belladonna	15	**1**	**1**	**7**	**6**	**48**
Placebo		*4*	*2*	*5*	*4*	*35*
Digitalis	19	**3**	**1**	**8**	**7**	**34**
Placebo		*4*	*2*	*7*	*6*	*25*

results obtained with certain drugs. We have attempted to face this problem by the introduction of control periods of treatment with a placebo. It is to be hoped that even longer periods of observation will be adopted in the future in order to determine the duration of such remissions and the factors which favour their appearance. Controlled investigation into continuous treatment would thereby gain in accuracy.

In 66 patients in our series who received placebo treatment only, 18 (27 per cent.) showed great improvement (*a*), and 7 (10·5 per cent.) showed moderate improvement (*b*). Table XIV and the graph illustrate how 9 of the 13 active drugs proved less efficacious than a placebo in reducing the frequency of the attacks. It is remarkable that placebo treatment gave better results than most of the active drugs, and appeared statistically to be the better form of treatment. Two factors probably contribute to this result. First, in the majority a placebo was the first medicine to be given at hospital,

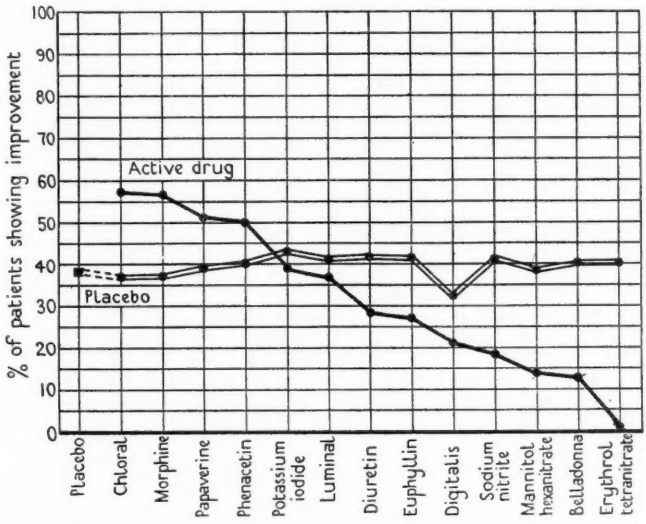

FIG. 1. Diagram showing comparative improvement in patients with angina pectoris from active drugs and placebo. Continuous line indicates improvement from active drugs. Double line indicates improvement from placebo in the same patients. Interrupted line indicates improvement in a standard series of patients treated with placebo.

so that mental suggestion apparently added bias in its favour. Secondly, placebo treatment was repeated more often than any single active drug, so that it coincided more frequently with a natural remission. In this event placebo treatment was continued until the attacks returned—when it became desirable to test other drugs. Although placebo treatment may not actually deserve first place because of these fallacies, none of the active drugs can claim precedence over it. If any drug had provided improvement greater than another, we might have accepted this as evidence of its value in continuous treatment, but such improvement did not occur.

At the same time it should not be assumed from these negative mass results that a particular drug may not have a beneficial effect in individual patients. Although we have shown that statistically and comparatively a particular drug is ineffective, we cannot deny that it may have a place in

treating the occasional individual. This is a poor argument, however, for a wider application in treatment, seeing that, with one exception, it applies to every drug we have tested, including the placebo.

If additional evidence were needed to confirm the failure of all the drugs tested, we would mention that our disappointment has been shared by the patients. None have insisted that any particular drug should be continued, and most of them still attend in the hope that some effective drug will be issued to them.

Summary

A series of 90 patients with angina pectoris of effort was observed over a period of two and a half years, with special reference to the comparative value of certain drugs used in continuous treatment. Syphilitic angina pectoris was excluded, and coronary thrombosis was only considered as a complication.

Each patient attended fortnightly, and the various drugs were administered over periods of two to four weeks at a time, or longer. In this way their effects upon the frequency and severity of attacks could be compared. As a control in each case a placebo was regularly substituted for an active drug. The following drugs were tested: sodium nitrite, mannitol hexanitrate, erythrol tetranitrate, potassium iodide, luminal, chloral, morphine, papaverine, phenacetin, diuretin, euphyllin, belladonna, digitalis, lacarnol, and harmol.

The comparative results are outlined in Table XIV and in the graph. With one exception, they show that a measure of improvement appears to result from every remedy tried, and at least as great an improvement during treatment with placebo. This universal efficacy can only be explained by natural variations in the severity of the symptoms, which give a spurious value to each remedy. If any drug had proved to be superior there might have been grounds for recommending it in the continuous treatment of the disease, but no such precedence could be made out. Though scarcely convincing, there was some reason to think that chloral, morphine, papaverine, and phenacetin had a trifling influence in controlling the group incidence and severity of attacks.

We have been unable to convince ourselves that any drug tested is worthy even of trial in the routine treatment of the disease. Though not widely applicable, a drug might of course be effective in individual cases, and examples were sought for, but, with a few exceptions, were not found. The nature of the underlying cause of angina pectoris alone would seem to make the quest for a satisfactory form of treatment on these lines unlikely of attainment.

If, as we are convinced, none of these remedies are capable of lessening the frequency or severity of anginal attacks, there is all the greater need for a study of the application of those general measures known to control them, and to promote the wider use of vasodilators, such as trinitrin, which

are so often successful in the palliative treatment or even in the prevention of particular attacks.

We wish to acknowledge great indebtedness to our chief, Dr. John Parkinson, whose encouragement, criticism, and help alone made this investigation possible. To other members of the Honorary Medical Staff, who allowed us to observe the treatment of their patients, we owe our best thanks.

This investigation was made while one of us (W. E.) worked under the Paterson Bequest to the Cardiac Department, and the other (C. H.) as Medical First Assistant to the Hospital and Gillson Scholar to the Society of Apothecaries.

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TWO CASES OF 'FATTY DIARRHOEA', WITH SPECIAL REFERENCE TO NITROGEN METABOLISM[1]

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With Plates 28–9

In recent years increasing attention has been paid to the group of diseases comprised under the term idiopathic steatorrhoea. Steatorrhoea, as a presenting symptom, is common to several different diseases which may present concomitant disturbances in haemopoeisis, in carbohydrate, calcium, and phosphorus metabolism. This group includes typical Gee-Herter or coeliac disease of children or adults, sprue, non-tropical sprue, as described by Thaysen, and pancreatogenous fatty diarrhoea. We exclude from this group malignant disease of the pancreas and acholic steatorrhoea. The literature of the subject has been admirably reviewed by Thaysen in 1926 (1), and by Bennett, Hunter, and Vaughan (2), in their recent publication, and by Thaysen (3) in his recent monograph.

It is not our purpose to discuss the vexed question of the similarity or differences between coeliac disease and non-tropical sprue on the one hand, or between non-tropical sprue and sprue on the other hand, although, from our experience of a small number of patients, we would incline to place cases where steatorrhoea occurs for the first time in adult life in individuals who have never resided abroad in the category of non-tropical sprue as described by Thaysen. In this group of cases Thaysen has emphasized the necessity for investigating the nitrogen metabolism in order to establish a differential diagnosis between non-tropical sprue and pancreatogenous fatty diarrhoea. He maintained that neither the clinical examination nor the routine laboratory tests, such as the detection of enzymes in the duodenal juice and stool, the nuclear test, and the examination of the ratio of unsplit fats to split fats in the faeces, were sufficient to establish a diagnosis of pancreatic disease, in any case under observation. But from the study of his own cases, and from data collected from the literature, Thaysen was of the opinion that the demonstration of a large percentage loss of nitrogen by the bowel was a strong argument in favour of a pancreatic lesion. In five of his own cases of pancreatogenous fatty diarrhoea he found, in two- to four-day

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observation periods, a percentage loss of nitrogen by the bowel varying from 8 to 97 per cent., while no values higher than 19 per cent. occurred in his cases of non-tropical sprue.

Apart from the work of this author, little attention has been paid to the excretion of nitrogen by the bowel as a diagnostic agent, nor indeed to the total nitrogen balance in cases of fatty diarrhoea. Bennett, Hunter, and Vaughan (2) did not investigate this aspect of the problem in their series of cases and found only the scantiest information relative thereto in their search of the literature. As stated by these workers, Herter found that the absorption of protein was diminished; McCrudden and Fales observed increased nitrogen in the faeces; Czerny et al. found a diminution of nitrogen content in the stools; Faconi also reported a considerable loss of nitrogen, but Schaap found no nitrogen loss in the faeces beyond what is to be expected when bulky fatty stools are prominent.

Bennett and his co-workers noted low values for blood-urea and non-protein nitrogen in several of their cases and attached some significance to this finding, particularly since a diet relatively high in protein was being given. Macrae and Morris (4) estimated the nitrogen excretion by the bowel in a series of observations in their cases of coeliac disease. The nitrogen percentage of the dried faeces seemed within normal limits, and any excess of nitrogen loss by the bowel was the result of increase in the total weight of the stool. In three instances a high percentage of nitrogen was found in the dried stool, when 19·4, 20·4, and 53·5 per cent. of the total intake of nitrogen was excreted in the motions. These results occurred simultaneously with defective absorption of fat, and it appeared to the authors that the absorption of protein was interfered with relatively and absolutely in the acute stages of the disease.

The metabolic balance experiments on two of our own cases of adult steatorrhoea described below were carried out to determine whether the importance placed upon increased faecal nitrogen loss by Thaysen could be relied on as a characteristic diagnostic factor between non-tropical sprue and pancreatogenous fatty diarrhoea. We were also interested to discover what effect failure of nitrogen absorption might have upon the total nitrogenous balance of the patients. It seems curious that so little attention has been paid to the maintenance of nitrogenous equilibrium in a condition where there is gross disturbance of the digestion and absorption of fat, particularly since it is evident that there is often present some degree of inability to utilize protein effectively. The maintenance of nitrogenous equilibrium in these cases seemed to us to be the most important single factor in the preservation of a satisfactory state of nutrition.

In the investigation of the cases special attention was paid to eliciting all information which might be of value in making a differential diagnosis. The character of the onset of the steatorrhoea assumes some importance. In cases of idiopathic steatorrhoea there is frequently present a history of long continued intestinal symptoms, sometimes dating back to infancy. This fact

has been emphasized by Bennett, Hunter, and Vaughan, and has led them to the opinion that coeliac disease and non-tropical sprue are virtually one disease seen at different times in its development. Thaysen drew attention to the same point in his cases of non-tropical sprue. But in some cases this evidence may be lacking or unconvincing. In our own cases there was no previous history suggestive of either long-continued diarrhoea or of intestinal disturbance in infancy. Where steatorrhoea occurs for the first time in adult life, or after years of good health, it is necessary to consider the possibility of failure of pancreatic function. This is particularly the case where attacks of upper abdominal pain have occurred, and especially where the bile-ducts and the stomach or duodenum have been the site of previous operative interference. Case 12 of the series of Bennett et al. must be included in this classification, and one of our own cases was the subject of a gastro-enterostomy and partial duodenal excision.

Loss of weight and abdominal distension may be common to both conditions at various phases of the disease. Absence of subcutaneous tissue and transparency of the skin are likewise common to both diseases. Atrophic glossitis is more frequently present in the cases resembling sprue. Achlorhydria may be present in either clinical picture, as may also anaemia, whether hyperchromic or hypochromic in character. Disturbances of calcium and phosphorus metabolism and skeletal changes may be present in both types of cases, although bony deformities are much more likely to occur in youth and adolescence. In our view the development of anaemia, of tetany, and of skeletal changes, are secondary to intestinal malabsorption.

The demonstration of tumour in the site of the pancreas, or of pancreatic calculi, by radiography is of diagnostic importance, as is also an increase in the quantity of serum bile-pigment as evidence of latent icterus. A blood-sugar curve of the diabetic type may indicate disturbance of the internal secretion of the pancreas, but is no evidence of failure of the external secretion of that gland, while a pancreatic lesion is not necessarily accompanied by hyperglycaemia. It seems clear, on the other hand, that permanent normoglycaemia is usually present in idiopathic steatorrhoea.

In the stool itself the presence of a large amount of unsplit fat, a small amount of soaps, and a large amount of undigested protein, is very suggestive evidence, according to Thaysen, of the presence of a pancreatic lesion, particularly if accompanied by diminished carbohydrate tolerance.

Case 1. The patient, a fisherman aged 34 years, was admitted to the Aberdeen Royal Infirmary in May 1930. He complained of attacks of diarrhoea which had commenced a year previously and lasted for a week at a time with intervals of four to five weeks of almost normal bowel movement. He noticed that a foul odour of the breath preceded the diarrhoea and remained during the attack. Recently the periods of diarrhoea had become more frequent, and the motions more offensive. He had been losing strength and weight. His appetite was sometimes good and sometimes poor. He had previously been a very healthy man, and had served in the Royal Navy during the war of 1914–18, but had not been out of home waters. He had

Table I

Protocol. Case 1

	Diet.			Nitrogen.						Fat in stool.					
	C.	P.	F.	Intake grm.	Urine grm.	Stool grm.	Total.	% loss by bowel.	Balance minus.	% dry weight.	Total. grm.	Neutral %	F.A. %	Soaps %	Loss %
Day 1	156·5	60·5	122	9·68	12·05	9·45	21·5	97·7	11·8	30	66·2	13·1	57·7	29	—
2	130·5	49	93·5	7·84	20·2	9·45	29·7	121	21·8	—	66·2	—	—	—	62
3	72·5	11	11.5	1·76	8·16	1·9	10·1	108	8·3	27·3	12·5	11·0	69·8	19·4	—
4	92	20	19·5	3·2	9·1	1·9	11·0	59·4	7·8	—	12·5	—	—	—	81
5	120	29	43·5	4·64	10·98	2·9	13·9	59·7	9·2	39·6	26·6	32·0	62·3	5·7	—
6	149·5	29	66·5	4·64	8·83	2·9	11·7	59·7	7·0	—	26·6	—	—	—	48
7	149·5	29	66·5	4·64	7·3	2·3	9·6	49·6	4·9	42·7	20·3	19·4	48·7	32·4	—
8	149·5	29	66·5	4·64	7·82	2·3	10·1	49·6	5·4	—	20·3	—	—	—	30
9	149·5	29	67	4·64	7·1	2·5	9·6	54	4·9	—	—	—	—	—	—
10	149·5	29	67	4·64	7·4	2·5	9·6	54	5·2	—	—	—	—	—	—

Analysis: 1. Great loss of urinary nitrogen.
2. High percentage loss of nitrogen by bowel.
3. High fat excretion. Fats well split.
4. High percentage of free fatty acids and low soap content.

never required medical attention until 1925, when he had a septic hand following injury with a fish-hook. In January, 1929, the patient noticed three small white pimples on his legs, and on the left leg an ulcer the size of a florin remained over the site of one of these for three weeks. The diarrhoea commenced after this time. One attack of acute abdominal pain of two hours' duration had occurred in March, 1930, while the patient was at sea, but otherwise he had no pains in the abdomen. He had never vomited and only once felt sick. He denied venereal disease. The family history revealed nothing relevant. The father of the patient was alive and well, as were five brothers. His mother died when the patient was 2 years old, and one sister died at 20 years of age of some acute illness, nature unknown.

The patient was moderately well nourished and of good colour, weight 129 pounds. The tongue was clean and showed no glossitis, and the throat was healthy. There were some bad teeth. There were no enlarged lymphatic glands. Nothing abnormal was found in the examination of the heart and lungs. The blood-pressure was low, systolic 95, diastolic 52 mm. Hg. The abdomen showed no distension and no localized swelling, and there was no tenderness on palpation. The spleen, liver, and kidneys were not palpable, and there was no enlargement of hepatic or splenic dullness. The examination of the spine was negative; there were no bony deformities. There was no abnormality found in the central nervous system. The left leg was slightly wasted and showed two pigmented scars. One similar scar, about the size of a shilling, was present on the right leg. The urine contained no albumin or sugar and the Wassermann reaction was negative. No pancreatic calculi were seen by X-ray examination of the abdomen, and a barium meal demonstrated normal motility of the stomach, duodenum, and intestine. There was complete absence of hydrochloric acid in the stomach contents in response to a test meal. The blood count showed, haemoglobin 85 per cent., red cells 2,500,000 per c.mm., white cells 9,800, colour index 1·7. The red cells showed well-marked megalocytosis. A sugar tolerance test showed a flat curve in response to 50 grm. glucose, fasting blood-sugar 0·090 per cent., later values at thirty-minute intervals being 0·090, 0·100, 0·085, 0·100 per cent. The blood cholesterol value was low, 108 mg. per cent., and the blood calcium 8·0 mg. per cent. The diastatic index of the urine was 50. The stool was pale in colour and offensive in odour, and weighed about 1½ lbs. daily. No tubercle bacilli were found at any examination, nor was monilia found. The benzidine test was negative. Microscopically the stool consisted largely of fat, mostly present as fatty acid crystals, but globules of neutral fat were also seen. Fragments of muscle showed very distinct striation and undigested nuclei were present. The fat content was 53 per cent. dry weight.

The patient was placed on a diet consisting of carbohydrate 200 grm., protein 66 grm., and fat 122 grm. The stool was collected in 48-hour portions, well mixed, weighed, and a sample taken for analysis. The stool was pale in colour, pultaceous, but not frothy. The average daily weight for the first four days was 30 ounces. There was no separation of oil on standing. Estimations were made of the stool content of total fat, neutral fat, free fatty acids, soaps, and nitrogen. Difficulty was found with the nitrogen determinations until a method was evolved for placing a weighed quantity of dried stool, contained in a small watch-glass, into the bottom of the digestion flask. The urine was collected in 24-hour periods for nitrogen estimation. An initial period of three days on the standard diet was allowed before collecting specimens of stool and urine.

The patient was unable to take all the protein and fat in the diet. He had a natural preference for carbohydrate food and the diet was later modified to 150 grm. carbohydrate, 29 grm. protein and 67 grm. fat. Table I contains the result of the experiment in this case.

An examination of the protocol shows that a condition of gross nitrogen imbalance existed during the whole experiment. Including urinary and faecal fractions, the average negative nitrogen balance was 8·6 grm. daily. The urinary nitrogen itself was greater than the intake, particularly during the early part of the test period. There was no complicating factor present to explain this phenomenon, and, in particular, there was no pyrexia to stimulate endogenous nitrogen metabolism. In spite of the negative balance it is interesting to note that the urinary nitrogen became practically constant during the last five days.

The nitrogen excretion by the bowel was excessive in the first two specimens collected. This was no doubt due to intestinal stasis and to the consequent discharge of faecal masses derived from the previous days. Although the percentage loss of ingested nitrogen by the bowel was greatest during the first three days, it remained still above normal in the later part of the experiment when the nitrogen intake was reduced. It is doubtful, however, if any significance can be placed on finding a loss of 50 per cent. of nitrogen by the bowel during a period of low nitrogen ingestion, since the normal faecal content in nitrogen must be taken into account. It is evident that the greatest faecal nitrogen excretion accompanied the days of highest fat excretion, and it is therefore possible to argue that nitrogen absorption failed during this time on account of the highly fatty nature of the intestinal contents.

The fat in the stool formed 27 to 42 per cent. of the dry weight. On the average only 18·8 per cent. was present as neutral fat, while 59·6 per cent. existed as fatty acids and 21·6 per cent. as soaps. It is possible to deduce from this only that fat-splitting was relatively good and that an active lipolytic ferment was present in the intestine.

The sum of the evidence in this case points to a diagnosis of idiopathic steatorrhoea or non-tropical sprue. Steatorrhoea was present, accompanied by megalocytic anaemia, increased tolerance for carbohydrate and achlorhydria. There was no jaundice or latent jaundice; the Wassermann reaction was negative and there was no evidence of a pancreatic tumour or pancreatic calculi. The nitrogen excretion by the bowel was increased, but little significance can be placed on this if the nitrogen intake is low, while we could not exclude the possibility of stasis in the early part of the experiment.

The patient died a year later in the country, and we were unable to get an autopsy to establish the diagnosis with certainty.

Case No. 2. The patient, a male tramway worker aged 31 years, was admitted to the Aberdeen Royal Infirmary in October 1930. He complained of diarrhoea and of an eruption on the face. The diarrhoea commenced about fifteen months previously with an occasional loose motion, but recently

there had been four or five bulky stools daily. He had never passed any blood, nor was the diarrhoea accompanied by abdominal discomfort. He had no sickness or vomiting and had not been jaundiced. His appetite was good, but he had been losing weight.

He had been a healthy man until 27 years of age and had seen service in the Royal Navy, but had never been abroad. He had never had dysentery or diarrhoea until the onset of the present illness. In 1926 he had indigestion and upper abdominal pain after eating. A diagnosis of duodenal ulcer was made and the patient underwent an operation in the wards of Sir John Marnoch. A hard, indurated area, 1·5 cm. in diameter, was seen on the wall of the duodenum 3 cm. from the pylorus. The gall-bladder and appendix were seen to be healthy. A posterior gastro-enterostomy was performed. One year later he vomited blood, and at a second operation an ulcer with cicatrization in the neighbourhood of the pylorus was found. The stoma was apparently normal. The ulcer was excised along with part of the pylorus. No abnormality of the faeces was noticed during convalescence. The patient enjoyed good health for about two years until the onset of the present complaint. The family history revealed no relevant information.

The patient weighed 115 pounds and looked undernourished. The skin was pale and dry and somewhat transparent and there was noticeable absence of subcutaneous fat. Sycosis of the bearded region was present, accompanied by blepharitis. The tongue was clean and the throat healthy. One septic tooth was present in the lower jaw; the upper teeth had been removed. There were no enlarged glands. The pupils were circular, equal, and reacted normally. The reflexes were normal. There was no abnormality found in the examination of the heart and lungs. There were no bony deformities and the examination of the spine was negative. The abdomen was generally protuberant and an upper paracentral operative scar was present. The spleen, liver, and kidneys were not palpable, nor were the splenic and hepatic areas of dullness increased in size. No tumour mass was palpable; no swelling could be felt in the site of the pancreas. The percussion note over the abdomen was hyper-resonant; both flanks were resonant. The urine, specific gravity 1025, contained neither sugar nor albumin nor any abnormal deposit. The diastatic index was 20 Wolgemuth units. The stools were pale, bulky, and pultaceous, but not frothy or particularly offensive. The fat content was 48·7 per cent., dry weight. Several examinations for organisms of the enteric and dysenteric groups were negative; tubercle bacilli were not found. A fractional test meal showed that free hydrochloric acid was present in the gastric contents to a maximum of 0·075 per cent. There was no blood and no lactic acid; bile was present in the gastric contents two hours after the test meal was given. The fasting blood-sugar was 0·075 per cent., and the blood-sugar increased to 0·141 per cent. thirty minutes after the ingestion of 50 grm. glucose and returned to normal value within two hours. The serum contained no excess of bile-pigment by the quantitative Van den Bergh method. The blood count showed, haemoglobin 90 per cent., red cells 4,870,000, white cells 6,600, with a normal differential count and no abnormal cells present. Examination of the abdomen by X-ray showed no evidence of pancreatic calculi and barium passed freely to the caecum when a barium enema was given, although the outlines of the sigmoid and descending colon appeared woolly and somewhat blurred.

The patient was given a standard diet containing 200 grm. carbohydrate,

TABLE II

Protocol. Case 2

	Diet.			Nitrogen.						Fat in stool.					
	C.	P.	F.	Intake grm.	Urine grm.	Stool grm.	Total.	% loss by bowel.	Balance minus.	% dry weight.	Total. grm.	Neutral %	F.A. %	Soaps %	Loss %
Period I	200	66	121												
Day 1	—	—	—	10·6	12·35	5·9	18·2	—	7·6	—	67·8	—	—	—	—
2	—	—	—	9·26	9.19	5·9	15·1	56	4·5	54·5	67·8	28·4	58·6	13·0	56
3	—	—	—	9·26	10·03	6·5	16·5	—	7·2	—	76·6	—	—	—	—
4	—	—	—	9·26	9·98	6·5	16·4	70	7·1	57·3	76·6	34·2	47·1	18·7	63
5	—	—	—	9·26	9·57	6·3	15·9	—	6·6	—	81·5	—	—	—	—
6	—	—	—	9·26	9.98	6·3	16·3	68	7·0	58·6	81·5	44·7	35·9	19·4	67
7	—	—	—	9·26	9·87	7·8	17·7	—	8·4	—	86·9	—	—	—	—
8	—	—	—	9·26	9·81	7·8	17·6	84	8·3	55·0	86·9	43·1	48·3	8·6	72
9	—	—	—	9·26	9·28	6·1	15·4	—	6·1	—	70·0	—	—	—	—
10	—	—	—	9·26	8·71	6·1	14·8	66	5·5	54·5	70·0	53·4	36·8	9·9	58
Period II	401	82	16												
Day 1	—	—	—	13·1	9·2	4·75	13·9	—	0·8	—	14·7	—	—	—	—
2	—	—	—	13·1	9·1	4·75	13·8	35	0·7	25·0	14·7	49·2	30·4	24·4	—
3	—	—	—	13·1	12·8	5·8	18·5	—	5·4	—	17·5	—	—	—	—
4	—	—	—	13·1	10·6	5·8	16·4	44	3·3	24·4	17·5	51·4	36·4	12·2	—
Period III	401	82	16												
1	—	—	—	13·1	10·5	5·7	16·2	—	3·1	—	11·6	—	—	—	—
2	—	—	—	13·1	10·2	5·7	15·9	43	2·8	18·2	11·6	43·0	50·0	7·0	—
3	—	—	—	13·1	9·6	7·1	16·7	—	3·6	—	14·1	—	—	—	—
4	—	—	—	13·1	9·3	7·1	16·4	54	3·3	19·6	14·1	37·0	53·7	9·3	—

Period III with pancreatic capsules.

Analysis: 1. Great loss of nitrogen by bowel. Increasing percentage loss during Period I.
2. Constancy of urinary nitrogen excretion during experiment.
3. Approach to satisfactory nitrogen equilibrium on high carbohydrate, high protein, and low fat diet.
4. Great fat loss by bowel.
5. Fat digestion fatigue during Period I. ? Diagnostic of pancreatic lesion.

66 grm. protein, and 121 grm. fat. He took this well, and a satisfactory experimental period was obtained. The protocol is presented in Table II. The urinary nitrogen excretion remained almost constant and the patient seemed to be almost on nitrogenous equilibrium during period I. When the excretion of nitrogen by the bowel is included, however, it is seen that an average negative nitrogen balance of 6·8 grm. was actually present, representing a loss of 42 grm. of endogenous protein daily. The average weight of the stool during this period was 1,162 grm. It contained a daily average of 6·5 grm. of nitrogen. The percentage loss of nitrogen by the bowel increased from 56 per cent. to 84 per cent., with an average of 69 per cent. The average absorption of nitrogen was 2·76 grm. daily. The fat content of the dry faeces remained very constantly near 56 per cent., but the total fat excreted increased during the time of the experiment from 68 grm. to 87 grm. daily. Along with this, an increase occurred in the amount of neutral fat and a parallel decrease in the percentage of free fatty acids and soaps. It would appear that there was present a continuous fatigue in fat digestion accompanied by an increasing failure in the digestion and absorption of protein. Impairment of proteolytic activity may not have been primary, but may have been consequent to the increasing fat percentage of the intestinal contents.

In period II the diet was changed to contain 401 grm. carbohydrate, 82 grm. protein, and 16 grm. fat, with practically the same total calorie value. After five days on this regimen, collection of urine and faeces was restarted. The result was a nearer approximation to the attainment of nitrogen equilibrium and a smaller excretion of nitrogen by the bowel, in spite of the greater protein content of the diet. The average daily absorption of nitrogen increased to 7·8 grm. for the four days of this test period. There was thus better utilization of protein when the diet was practically fat free, showing that a large percentage of fat in the intestinal contents interfered with protein metabolism, whether primary failure of this function was present or not. In period III a pancreatic preparation in capsules was given by mouth, but with no improvement.

The general condition of the patient was much better on a high carbohydrate diet with liberal protein intake and the minimum of fat. The diarrhoea stopped. The average daily weight of the stool was now 448 grm. With suitable local applications the skin condition cleared up and the patient was discharged well.

A diagnosis of pancreatogenous fatty diarrhoea was made for two main reasons. It seemed possible that the onset of diarrhoea was related to operative interference in the region of the duodenum, and, if this were so, partial cicatricial occlusion of the pancreatic ducts might explain the pathology of the condition. High excretion of nitrogen by the bowel, even on a practically fat free diet, strongly suggested diminution or absence of the external secretion of the pancreas, particularly when hydrochloric acid was known to be present in the gastric contents.

The patient was readmitted to the skin wards of the hospital in April 1931, with recurrence of sycosis. A typical sycotic eruption was present affecting the whole of the bearded region and upper lip. There was uniform redness with localized pustular hair roots, from which *Staphylococcus aureus* was cultured. An autogenous vaccine was given. Almost complete cure resulted, and the patient was discharged. He was readmitted in August 1932 with boils on the right leg. He had lost twenty-three pounds in weight and his general condition had deteriorated. His appetite was poor and he had been unable to take his diet. Diarrhoea was again present with periods of abdominal distension and vomiting. The patient wasted rapidly and developed a cough with sputum. No tubercle bacilli was present in the sputum or stool. A terminal basal pneumonia occurred and the patient died on 28th November, 1932.

Post-mortem examination, 29.11.32. Summary of lesions: Marked emaciation; gastro-enterostomy; colloid goitre; acute broncho-pneumonia both lungs; acute fibrinous pleurisy.

Report, abbreviated: Subcutaneous fat practically absent, marked wasting of skeletal muscles. Old paracentral scar in upper abdominal wall. No oedema. jaundice, or skin haemorrhages.

No free fluid in peritoneal cavity.

Catarrhal gastritis (slight), posterior gastro-enterostomy of which the stoma was contracted but still admitted two fingers. No evidence of recent or old ulceration of stomach or in neighbourhood of gastro-enterostomy.

No pyloric or duodenal stenosis.

Some scarring and adhesions in relation to first part of duodenum between it and pancreas and extending into gastro-hepatic omentum. Appendix slightly atrophic and retro-caecal. Gall-bladder and ducts were healthy to the naked eye.

No important naked eye changes in pancreas.

Microscopic examination of pancreas.—The principal change was increase of dense fibrous connective tissue at surface of pancreas in relation to and surrounding the splenic artery, also extending into the adjoining pancreas and causing local atrophy of lobules.

Great thickening round all large and small ducts, extending deeply into the organ; the fibrous tissue ending in firm branchings which penetrated at times intimately the parenchyma, separating off lobules of this, which were undergoing atrophy. Only occasionally could one see islets surrounded by the connective tissue.

Large areas of the pancreas showed little alteration, apart from thickening round the ducts; but in one or two parts one could detect retention cysts. (See micro-photographs.)

Discussion

A discussion of the differential diagnosis in the two cases described centres round the interpretation which can be placed on abnormal nitrogen content of the stool. In the healthy individual the stool rarely contains more than 2·5 grm. of nitrogen daily, irrespective of the nature of the diet.

Martin and Robinson (5), in their experiments on minimum nitrogen expenditure, noted that the stool contained from 1·05 to 1·17 grm. nitrogen when the daily intake of nitrogen was in the neighbourhood of 0·3 grm. and the diet adequate in caloric value. On diets containing 8 grm. nitrogen daily, mostly as wheat, the stool contained as much as 2·35 grm. nitrogen daily, with the individual on nitrogen equilibrium. Where milk formed the source of ingested nitrogen the faecal nitrogen did not exceed 1·4 grm. daily. The character of the food nitrogen has, therefore, some influence on the digestion and absorption of that element. Smith (6) also noted that on diets of minimal nitrogen value (0·06 to 1·05 grm. daily) the stool contained from 0·73 to 0·91 grm. nitrogen. On unrestricted diets in the same subject the stool contained an average of 1·03 grm. nitrogen daily. Figures quoted by the same author from the publications of Rubner, Rieder, Landergren, and Siven show that on diets containing under 3 grm. of nitrogen, the stool content varied from 0·22 to 1·47 grm. daily. Smith suggested that the variation in the nitrogen content was due more to intestinal secretions and cellular debris than to food residue. In diets higher in nitrogen content there is no relative increase in faecal nitrogen. Pierce (7) found that in diets containing up to 85 grm. protein daily, the stool never contained more than 1·8 grm. nitrogen, although, if yeast were added to the diet, values up to 2·4 grm. daily were found.

From the work of these authors we can assume that, even on a diet which is practically nitrogen free, the stool may contain 1 grm. of nitrogen daily, and that where the nitrogen content of the diet is abundant and not easily digested, the stool nitrogen does not exceed 2·5 grm. per day. Total nitrogen excretion in excess of 3 grm. daily in the stool is certainly pathological. The method of expressing the excretion as a percentage of intake may be misleading, since this figure may be very high if the nitrogen content of the diet is low. The general statement that excretion of over 25 per cent. of ingested nitrogen is pathological would hold true if the intake were over 8 grm. daily.

It is well recognized that in disturbance of the intestinal tract a number of factors can cause some increase in the amount of nitrogen excreted in the faeces. Achlorhydria, rapid peristalsis, copious intestinal secretions, and diminished fat absorption may all play a part, although no actual failure of protein digestion and absorption is present. It thus becomes a matter of some difficulty to assess the significance of increased amounts of nitrogen in the faeces. Failure of fat absorption has been of greatest importance in this respect in the investigation of the cases at present under consideration. From our own experience, and from figures collected from the literature, it would seem that this factor has a variable influence in preventing effective digestion and absorption of protein.

Thus Freise and Jahr (from tables quoted by Lehndorff and Mautner (8)) found that in two cases of coeliac disease in children, the stool contained 0·84 and 0·72 grm. nitrogen daily, while the stool in two healthy children

on the same diet contained 0·53 and 0·52 grm. daily. This occurred in spite of the fact that the coeliac patients excreted 81 and 68 per cent. respectively of the 56 grm. fat which the diet contained. The figures given by the same authors show that on a normal mixed diet containing 25 to 29 grm. protein and 27 to 42 grm. fat, the faeces in two cases of coeliac disease contained only 1·9 to 3·4 grm. protein, while 18 to 31 grm. fat were excreted. On the other hand, from a study of a table constructed by Thaysen (1) from his own investigations and those of other workers on cases of pancreatogenous fatty diarrhoea, one is led to conclude that there is no direct relation between the amount of nitrogen excreted in the stool and its fat content. This variable can, however, be eliminated by placing the patient on a diet deficient in fat, as was done in our second case. If the nitrogen content of the stool remains high under this régime, the finding assumes definite importance in diagnosis. Although the method of investigation is laborious, we agree with Thaysen that it is possible to differentiate between idiopathic steatorrhoea and fatty diarrhoea of pancreatic origin by this means.

Summary

1. Two cases of fatty diarrhoea in adults are described.

2. Records of the investigation of nitrogen metabolism are presented. It is noted that both cases showed gross negative total nitrogen balance.

3. One of these cases we believed to be idiopathic fatty diarrhoea and the other pancreatogenous fatty diarrhoea. The chief points in the investigation are summarized as follows.

Idiopathic steatorrhoea.	Pancreatogenous fatty diarrhoea.
Achlorhydria	HCl present in stomach
Megalocytic anaemia	Secondary anaemia
No pancreatic tumour or calculus	Pancreatic fibrosis
Flat blood-sugar curve	Normal blood-sugar curve
Gross negative total nitrogen balance	Gross negative total nitrogen balance
Faecal nitrogen less than 3 grm. daily	Excessive excretion of faecal nitrogen on fat-free diet
	Faecal nitrogen greater than 3 grm. daily
Fatty diarrhoea	Fatty diarrhoea with fat digestion fatigue

4. High nitrogen excretion by the bowel is shown to be a diagnostic factor of importance in the recognition of a pancreatic lesion.

We have to thank Professor Shennan of the Pathology Department, Aberdeen University, for the post-mortem report of Case 2, for the microphotographs, and for his help in the elucidation of the lesions in Case 2. We are also indebted to Sister Stephen of the Aberdeen Royal Infirmary for painstaking collaboration in the metabolic experiments.

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FIG. 1. Great increase of connective tissue about a large duct with proliferation and atrophy of epithelium. × 68

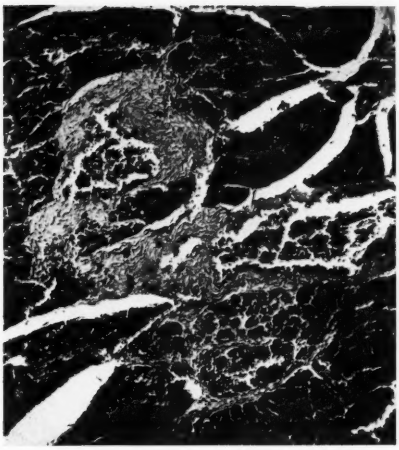

FIG. 2. Connective tissue round smaller duct with extension thence into neighbouring parenchyma. × 68

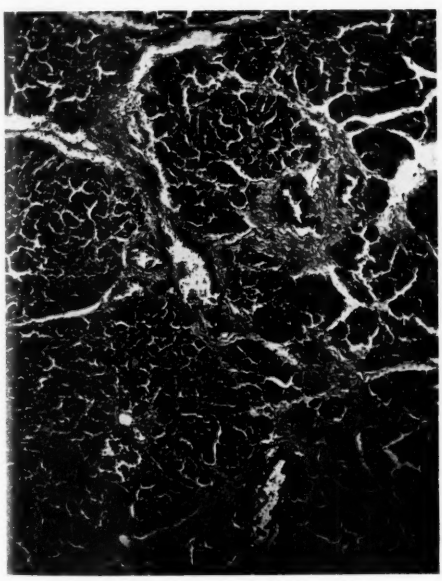

FIG 3. More diffuse extension of fibrous tissue involving small ducts and alveoli. × 68

FIG. 4. Diffuse connective tissue in parenchyma. × 68

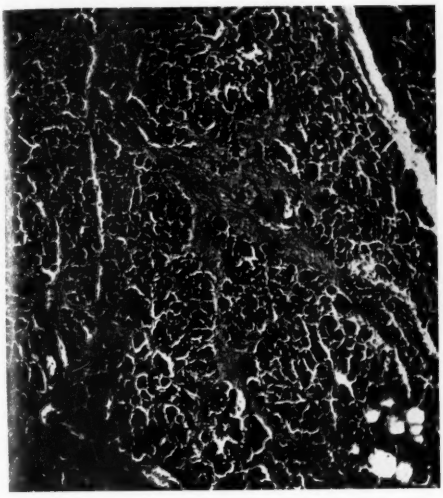

FIG. 5. Similar to last, but showing atrophy of pancreatic alveoli. × 68

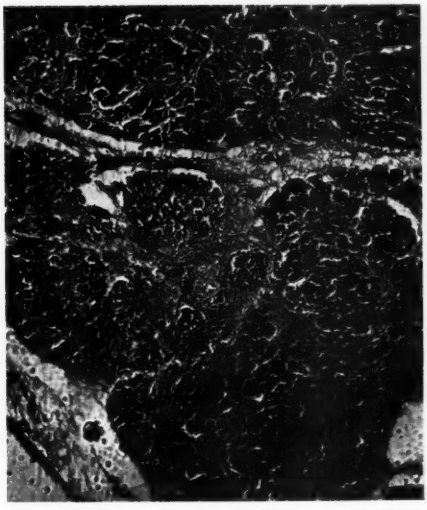

FIG. 6. Similar to last two. × 68

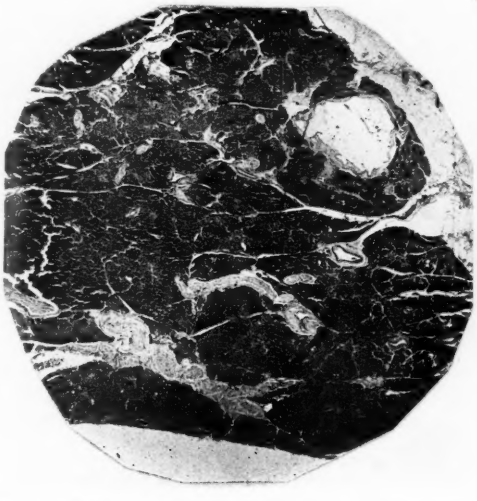

FIG. 7. In lower part of figure, two nerves resembling increase of connective tissue along septa. In upper part of figure, patchy increase of connective tissue chiefly along septa. In upper right quadrant, a small cyst with thick fibrous walls. × 8

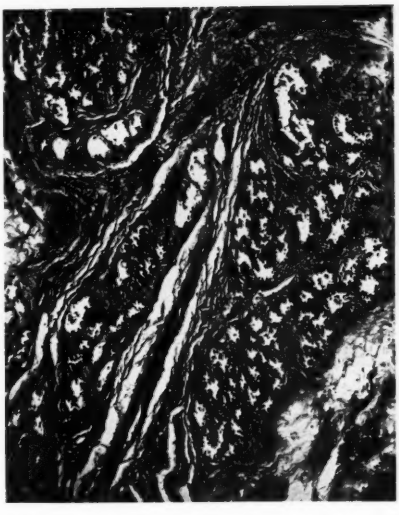

FIG. 8. A section of pancreas in neighbourhood of scar tissue on upper surface of head of pancreas showing great increase of connective tissue and atrophy of alveoli embedded in it. × 68

616.633.66
618.3

DIABETES MELLITUS AND PREGNANCY[1]

A CLINICAL AND ANALYTICAL STUDY

(WITH SPECIAL OBSERVATIONS UPON THIRTY-THREE CASES)

By ERIC SKIPPER

(From the Diabetic Department of the London Hospital)

During the last few years the writer has been able to observe in the Diabetic Department of the London Hospital a number of cases of diabetes mellitus with pregnancy. A knowledge of this condition is now more than ever of great importance, for pregnancy in the diabetic can no longer be considered a rare phenomenon. Since the introduction of insulin there has been a gradual increase in the volume of literature upon the subject. The number of cases upon which authors have based their conclusions has, however, been small, with the inevitable result that various misconceptions have arisen. Perusal of the modern literature reveals that the results of pregnancy in the diabetic have hitherto been disappointing, cases reported from most sources showing a persistently high foetal mortality in spite of the employment of insulin. The successful management of diabetes during pregnancy is often difficult and necessitates on the part of the physician familiarity with the influence of gestation upon the disease. With these considerations in mind it was thought that a review of the whole problem of the pregnant diabetic would be of value. Since 1923, i.e., since insulin has been generally available, 37 pregnancies have occurred in 33 diabetic patients at this hospital. From papers published since 1923 the writer has been able to collect details of 118 other cases (136 pregnancies). It is upon these two groups of cases that this communication is chiefly based.

The Maternal and Foetal Mortality; the Influence of Insulin

Bennewitz in 1826 was apparently the first to record an instance of a pregnant diabetic. This was a woman who suffered from intense thirst and polyuria during three successive pregnancies. Bennewitz states that 'the taste of the urine resembled beer but was much sweeter' and that the urine contained 'two ounces of saccharine matter per pound'. A second case was published by Lever in 1847, but it was not until 1909 that the late Whitbridge Williams was able to present in his well-known paper a summary of

[1] Received April 12, 1933.

a comparatively large number of cases. In his series of 66 pregnancies in 43 diabetics 27 per cent. of the mothers died during labour or the puerperium, generally from diabetic coma, and a further 23 per cent. succumbed during the succeeding two years. The foetal mortality, including abortions, was 41 per cent. Whitbridge Williams (1930) later suggested that these figures exaggerated the mortality, as probably some of the milder cases of diabetes in which pregnancy was uneventful did not appear in the literature. Nevertheless, it is obvious that before the discovery of insulin pregnancy in the diabetic was accompanied by grave danger for both mother and child.

Interest in the subject was naturally revived with the introduction of insulin, Graham being the first in this country to record the case of a pregnant diabetic treated with insulin. By 1928 various papers had appeared, the most comprehensive being that of Wilder and Parsons who discussed the results of 55 pregnancies in 51 diabetics, including 7 patients of their own. The maternal mortality was 12 per cent. and the foetal 47 per cent.[2] The 118 cases collected from the literature by the writer show a maternal mortality of 9·3 per cent. during pregnancy or the puerperium; diabetic coma, as in Whitbridge Williams' series being the chief cause of death. A further 3·4 per cent. of the mothers are said to have died within two years of delivery. The foetal mortality, including abortions, stillbirths, and babies dying shortly after delivery, was 45·2 per cent. (See Table II.) The writer has ignored a few cases in which the diagnosis of diabetes appeared to be doubtful.

If these figures are compared with those originally given by Whitbridge Williams, it will be evident that although insulin has considerably improved the outlook for the pregnant diabetic so far as her own life is concerned, it has not brought about any decrease in the foetal mortality. Among the London Hospital cases, which are summarized in Appendix II, there were no maternal fatalities during pregnancy or the puerperium, but 2 patients died eighteen months and five years respectively after childbirth. The high foetal mortality (40·5 per cent.) is partly due to the carrying out of therapeutical abortion in 3 cases, although there now seems to be no reason why these patients could not have continued successfully to full term. It may here be mentioned that in the group of 13 diabetics treated with special care on the lines to be later described, only 3 children were lost. (Cases Nos. 21–3.)

Insulin and the Fertility of the Diabetic

The diabetic, it has been alleged, does not often become pregnant. The reasons for this would appear to be two; first, the peak of incidence of the

[2] Joslin in 1928 recorded 89 pregnancies in 57 diabetics. The foetal mortality was 53 per cent., but the maternal mortality is not given. Many of these pregnancies occurred in pre-insulin days and the patients treated with insulin are not specified. These cases, details of which are unavailable, are not included in this paper.

disease amongst adult females coincides with the menopause (46), and second, amongst diabetics there is often a lack of potential fertility as judged by the frequency of disturbance of menstruation including amenorrhoea. The incidence of the latter was placed at 50 per cent. by Parisot who claimed to show that it was associated with disappearance of the Graafian follicles. Von Graefe had previously demonstrated atrophy of the uterus in diabetics.

That insulin may increase the fertility of the diabetic is suggested by the not infrequent return of menstruation in patients treated with insulin, even after lengthy periods of amenorrhoea. Joslin quotes some examples, but states that he only saw one such instance in pre-insulin days. The writer has observed a diabetic in whom the catamenia, absent for ten years, returned when the patient was given insulin. Fitz and Murphy and Bowen each report a case in which amenorrhoea of two years' duration was followed, after treatment with insulin, by menstruation, and later by pregnancy. Some idea of the rarity of pregnancy in the diabetic before the days of insulin may be gathered from the fact that Lecorché reported only seven gestations in 114 female diabetics, while Von Noorden before 1909 had observed only 5 per cent. of pregnancies in 427 diabetics of child-bearing age.

Up to the present there have been no available data from which the effect of insulin upon the fertility of the diabetic can be estimated. The following will therefore be of interest. During the years 1893–1922, 190 married diabetics up to the age of 46 years were admitted to this hospital, and of these 4 (2 per cent.) were pregnant. From 1923–31, 177 were admitted and 27 (15 per cent.) were pregnant. Sixteen patients became pregnant while receiving insulin, 10 of these for the first time since the onset of the disease. These statistics do not, of course, include patients in whom diabetes arose during the course of pregnancy. The chief criticism to which these figures are subject when regarded as an index of the influence of insulin upon fertility is that cases of mild diabetes are probably now diagnosed with greater regularity than formerly, and pregnancy occurs more often in them than in severe cases. Nevertheless, it is obvious that this consideration cannot account for the more than seven-fold increase in the incidence of pregnancy in the second group of patients. The diabetic woman of to-day frequently remains sterile, especially when the disease is of long duration, but there is no doubt that her chances of conception have been materially increased by insulin.

The Influence of Pregnancy upon Diabetes

The majority of the patients entered hospital for periods of observation during pregnancy and after delivery, and between admissions they attended the Out-patient and Antenatal departments. All childbirths save one took place in hospital. The routine observations carried out upon the patients

while in the diabetic wards included examination of 24-hourly specimens of urine for sugar with Benedict's qualitative reagent, and for ketones by Gerhardt's and Rothera's methods. All blood-sugars were estimated by a modification of the Folin-Wu technique, using 0·2 c.c. of capillary blood. In the series of 13 cases treated with especial care, during the 'balancing' of the diabetes the blood-sugar was estimated at two-hourly intervals from 6 a.m. to 9 p.m. on one or more days. It was found that more thorough control could be obtained by the use of these two-hourly blood-sugar readings than by single estimations. This procedure was repeated at intervals of from two to three months throughout pregnancy.

Sugar-tolerance tests were used, both for diagnostic purposes and for demonstrating changes in the renal threshold for dextrose. Fifty grm. of glucose, dissolved in two-thirds of a tumbler of water, were given by the mouth, the patient having fasted overnight. Specimens of blood and urine were taken simultaneously before administering the glucose and at half-hourly intervals afterwards for three hours. When the test was used to determine alterations in the threshold, the urine collecting in the bladder during the night was voided and discarded. It is not claimed that these sugar-tolerance curves give the true threshold, the estimation of which is a tedious process involving continuous catheterization. Nevertheless, it was found that the influence of pregnancy upon the threshold could be satisfactorily shown by this simple method.

I. *Changes in tolerance.*

(a) *During pregnancy.* Sufficient observations were made during 18 pregnancies in 17 women to enable changes in tolerance to be assessed. These cases were all followed throughout pregnancy or from the earliest months. Alterations in the severity of the disease were estimated by comparing the diet and insulin prescribed at various periods, those during which the patients were stabilized with normal blood-sugars being chosen for comparison whenever possible (see Appendix I). During 13 of these pregnancies the diabetes undoubtedly became worse, necessitating an increase in the dose of insulin. Infections and irregularities in diet and insulin probably contributed to the loss of tolerance sustained by 4 of these patients but, except for Case No. 26, the general course of events, especially the improvement during the puerperium, makes it unlikely that these factors were alone responsible. Case No. 26, which, incidentally, is a good example of the dangers of infection during pregnancy in a diabetic, went through the gestation period with tolerance unchanged until an influenzal attack precipitated glycosuria and the birth of a macerated child. She noticed that the foetal movements suddenly ceased when she was taken ill. The loss of tolerance, which was most pronounced in patients with the severer degrees of diabetes, usually occurred during the sixth or seventh month. In 4 patients tolerance remained unaltered during pregnancy. In Case No. 10 an apparent improvement took place during the eighth month, and it was then possible to increase the diet by over 500 calories and to

diminish the insulin by one-half. Much has been written about the improvement in the metabolism of diabetics during gestation, although this phenomenon has only been observed in a small percentage of cases. The best examples have been cited by Wilder and Parsons, Peckham, and Lawrence. Lawrence's case, a twin pregnancy, is the most convincing and showed a gain in tolerance from the twenty-eighth to the thirty-fourth week estimated at 100 grm. of carbohydrate. Peckham alleges that a gain in tolerance is actually to be expected as term is approached. There is no justification for this statement, as there is no doubt that an increase in the severity of diabetes during pregnancy is much more common. There have been many attempts to prove that any increase in tolerance is due to the transference of insulin from foetus to mother, the foetal pancreas partially compensating for the diminished production of insulin by the diabetic mother. Thus, the hypertrophy of the islands of Langerhans of foetuses born of diabetics has been interpreted by many as evidence of a compensatory process in this sense. There is, however, a more logical explanation of these pancreatic changes (*vide infra*). Metabolic details of the rare cases in which foetal island hypertrophy has been observed are scanty, but the case reported by Gray and Freemster is said to have gained tolerance between the fourth and eighth months.

In connexion with the problem, the experiments of Carlson and his co-workers have been widely quoted. Carlson found that usually complete pancreatectomy in pregnant bitches, if performed near term, resulted in little hyperglycaemia until labour, which was followed by a pronounced rise in the blood-sugar. He therefore concluded that during pregnancy foetal insulin entered the maternal circulation. Lafon confirmed these results, but Allen was unable to do so and suggested that Carlson's findings were the outcome of cachexia in his animals. Of more value, because more closely related to clinical diabetes, is the work of Markowitz and Soskin and of Macleod who showed that the carbohydrate balance of depancreatized dogs receiving insulin remained unchanged when the animals became pregnant. Thus experimental evidence, although conflicting, tends to show that, in the artificially produced diabetes of animals at least, no gain in tolerance occurs during gestation. There seems to be no doubt that insulin is capable of passing through the placenta, for Pack and Barber produced considerable lowering of the blood-sugar of goats far advanced in pregnancy by injecting insulin into the foetus *in utero*. Even so, there is little evidence that the foetal insulin is responsible for the improvement in carbohydrate metabolism which has occasionally been observed during pregnancy in human diabetics. It should be pointed out that any improvement may be merely the result of treatment, for diabetics frequently gain tolerance after a period of strict dieting and insulin therapy. In certain patients this might overshadow the tendency for the disease to undergo an exacerbation during gestation.

(b) *After delivery.* A gain in tolerance often occurs after childbirth,

particularly in severe diabetics, and was noted in 19 of the 33 hospital cases going to term or near it. Following delivery, in cases treated with insulin, the blood-sugar is usually low, symptoms of hypoglycaemia necessitating a reduction in the dose of insulin being extremely common. Insulin reactions, usually commencing during the first few days of the puerperium, occurred in 17 of the 23 patients who were receiving insulin at delivery. Hypoglycaemic coma was observed in three instances, although in Case No. 9 this was precipitated by an accidental overdose of insulin. Hypoglycaemia during the puerperium was apparently the cause of the maternal death reported by Kaufman and Küster.

Many writers allege that the hypoglycaemia is due to withdrawal of glucose from the blood by the breast in the process of milk formation (65, 81, 115). In support of this explanation they quote the work of Widmark and Carlens who claimed to show that the 'milk-fever' or 'parturient paralysis' of heavily milked cows is due to a hypoglycaemia. But those who attempt to explain the puerperal hypoglycaemia of diabetics on these lines are apparently unaware of the work of Dryerre and Greig and of Little and Wright who have proved conclusively that the symptoms of 'parturient paralysis' are due to a hypocalcaemia and not to a hypoglycaemia. The condition is, in fact, one of tetany. Mammary inflation, a form of treatment practised for many years, exerts its beneficial effect upon the disease not by increasing the blood-sugar, as Widmark and Carlens supposed, but by raising the blood-calcium. The blood-sugar in 'milk-fever' has indeed been found to be frequently high (25, 39, 40, 71). Although it may contribute to it, it therefore seems very improbable that lactation is the chief cause of puerperal hypoglycaemia. In further support of this is the fact that in only 2 of the hospital cases in which puerperal hypoglycaemia was observed had nursing been allowed. Moreover, the gain in tolerance following delivery is often maintained indefinitely, the condition of the patient reverting to that before pregnancy, and in no patient who had breast-fed her child was it found that the diabetes increased in severity at weaning. As possible temporary contributing causes of puerperal hypoglycaemia may be mentioned the replenishment of glycogen reserves following the exertions of labour and the small diet usually taken at the time of delivery.

The question of whether pregnancy may be permanently harmful to the diabetic has often been raised. Case No. 12, who had not been well controlled when pregnant and who did not receive insulin, lost tolerance progressively after childbirth, becoming a severe diabetic. Pregnancy did not appear to exert any lasting ill effect on the metabolism of any of the other patients. Following various infections and irregularities in treatment three patients are now in worse condition than before conception, and two have died, but no evidence is forthcoming that pregnancy was responsible for these misfortunes.

II. *The renal threshold.* Renal glycosuria, due to lowering of the renal threshold is not uncommon during pregnancy, but the proportion of pregnant

TABLE I

TABLE I

The Renal Threshold

Case no.	Duration months.	During pregnancy. Blood-sugars mg. %. Minutes. 0	30	60	90	120	150	180	Interval.	After delivery. Blood-sugars mg. %. Minutes. 0	30	60	90	120	150	180
		+	+	+	+	+	+	+		n	n	+	+	+	+	+
18	7	130	190	220	240	240	238	202	11 months	140	200	250	280	331	293	221
		+	+	+	+	+	+	+		t	t	t	t	n	n	n
20	9	127	243	243	238	210	178	152	4 weeks	152	200	234	210	191	176	166
		+	+	+	+	+	+	+		n	n	+	+	+	+	+
21	2	120	125	150	170	201	200	170	14 weeks	170	200	205	270	260	192	143
		t	+	+	+	+	+	+		n	+	+	+	+	+	+
25	6	124	175	210	224	234	165	165	10 weeks	161	190	243	249	246	208	204
		+	+	+	+	+	+	+		t	t	+	+	+	t	t
27	7	114	182	205	161	131	94	87	10 weeks	200	262	302	201	166	133	117
		+	+	+	+	+	+	+		t	t	+	+	t	t	
,,	9	138	202	232	222	182	122	102	25 weeks	174	250	266	286	201	166	—
		+	+	+	+	+	+	+		t	t	t	t	t	t	t
28	7	170	216	258	266	264	216	180	8 weeks	142	150	166	198	202	200	197
		n	+	+	+	+	+	+								
29	2	122	234	224	180	142	102	106	—	—	—	—	—	—	—	—
		+	+	+	+	+	+	+								
,,	4	91	156	173	168	143	104	86	—	—	—	—	—	—	—	—
		+	+	+	+	+	+	+		*+	+	+	+	+	+	+
,,	6	106	201	234	174	132	102	95	13 days	109	143	181	165	127	83	69
		+	+	+	+	+	+	+		n	n	n	n	n	n	
,,	9	103	142	218	264	160	108	97	7 weeks	118	217	250	137	90	81	—
		n	n	n	t	t	t	t		n	n	n	n	n	n	n
30	8	178	246	289	322	297	252	231	17 weeks	107	272	182	196	190	129	120
		n	n	n	n	n	n	n		n	n	n	+	+	+	+
31	8	80	138	154	128	127	117	99	11 weeks	70	221	280	277	251	187	140
		n	n	n	t	t	t			n	n	n	n	n	n	n
32	8	154	222	225	221	220	160	—	5 weeks	182	259	306	328	300	228	—
		+	+	+	+					n	n	+				
33	6	123	166	200	222	—	—	—	8 days	153	180	200	—	—	—	—

This table illustrates the fall in the renal threshold of diabetics during pregnancy and the rise after delivery. The blood-sugar was estimated before and at 30-minute intervals after 50 grm. of oral glucose. The traces of sugar in the urine on the ascending limbs of certain curves taken after delivery were in all probability lactose, and have no bearing on the threshold level. These cases were lactating. Many of the curves were modified by treatment and some thus show only a small rise.

Urinary sugar (Benedict) n = none; t = trace; + = well-marked reduction. * Urinary sugar proved to be glucose.

women who exhibit it has not been definitely determined. Neither is it certain at what period of gestation the alteration in the threshold most commonly occurs. From Table I it will be seen that a low threshold was present in at least 6 out of 11 diabetics during pregnancy. It is interesting to note that the threshold was well above normal in two patients and remained thus after delivery. Case No. 29 admirably illustrates that the threshold does not necessarily rise immediately after labour. Faber quotes a similar instance in a non-diabetic.

III. *Ketonuria.* There is, during uncomplicated pregnancy, no excess of ketone bodies in the blood (51, 76, 101). Nevertheless, ketosis is relatively more easily produced in pregnant women than in non-gravid persons by starvation, by diets containing large amounts of fat, or when nausea and vomiting interfere with feeding (9, 10, 37, 38). The reason for this is unknown, but it has been suggested that the pregnant woman may, like the infant, spend her liver glycogen with more than usual rapidity when deprived of exogenous carbohydrate, or that her liver may contain less than the normal amount of glycogen (95). It is obvious that the pregnant diabetic is especially prone to ketosis, for she is already suffering from a disease characterized by defective utilization of carbohydrate and incomplete oxidation of fat. When not efficiently treated she is peculiarly liable to develop diabetic coma, which is still to-day her greatest source of danger.

As judged by a positive Gerhardt's test, ketonuria was severe at some period during 17 or nearly half of the pregnancies in the London Hospital series, and 3 patients, 2 of whom subsequently proved to be very mild diabetics, developed diabetic coma when pregnant. The ketosis was generally most pronounced after the sixth month, but was occasionally well marked early in gestation. Examination of the diets prescribed reveals that usually the proportion of fat to carbohydrate must be decidedly low if ketosis is to be avoided. Provided that the blood-sugar is normal, the non-gravid diabetic will not, as a rule, excrete ketones on a diet furnishing a fatty acid : glucose ratio of 1·5 : 1, and ratios considerably higher than this are frequently tolerated. But during pregnancy it is often necessary to lower this ratio to well below 1 : 1, even if insulin is given and the blood-sugar is well controlled. Thus, Case No. 29 showed severe ketonuria throughout pregnancy on a FA : G ratio of 1 : 1·1, although the blood-sugar was always within normal limits, and ketonuria was persistent in Case No. 28 even with a ratio of 1 : 1·3 and insulin. These observations are not in agreement with those of Wilder and Parsons, who concluded that their patients did not evince any special tendency to ketosis. As emphasized by Rosenberg, a remarkable feature of the ketosis is the rapidity with which it invariably disappears immediately after delivery. It was not found that childbirth in the hospital cases was accompanied by any increase in the severity of the ketosis.

The Causes of Foetal Death in the Diabetic

I. *The control of the disease.* By far the most important cause of foetal death is neglect of the diabetes, especially during the latter months of pregnancy, and excluding all other possible factors this was responsible for 56 per cent. of the child fatalities in the collected cases and for 53 per cent. in the London Hospital series. In the badly treated diabetic the child is frequently born dead, often in a macerated condition, a few weeks before term, abortion in early pregnancy being relatively uncommon. The latter months of pregnancy are the most vital to the child, for inefficient control of the diabetes, even in mild cases, is then particularly liable to be accompanied by a rising blood-sugar and increasing ketosis in the mother; and such events are often followed by the death of the foetus in utero. It is because the importance of rigid control of the blood-sugar has not been sufficiently realized that the foetal mortality in insulin-treated cases has been so high.

TABLE II

The Foetal Mortality in Diabetics

	Collected cases.		Hospital cases.	
	No. of pregnancies.	Foetal mortality %.	No. of pregnancies.	Foetal mortality %.
Onset of diabetes.				
Before pregnancy	95	46·3	29	44·8
During pregnancy	33	39·3	8	25
Unknown	8	62·5	—	—
Degree of diabetes.				
Severe	24	70·8	8	62·4
Moderate	62	43·5	15	40
Mild	40	32·5	14	28·5
Unknown	10	50	—	—
Control of diabetes.				
Good	*60	16·6	*20	15
Indifferent	41	68·2	15	66·6
Untreated	20	90	2	100
Unknown	15	40	—	—

Collected cases: 136 pregnancies in 118 women. Foetal mortality = 45·2 %.
Hospital cases: 37 pregnancies in 33 women. Foetal mortality = 40·5 %.

* These figures include a few cases in which the diabetes was well controlled during the last two months of pregnancy only.

Table II shows the foetal mortality in relation to the apparent onset of the disease, its severity, and its control by treatment. It corroborates the view expressed by many of the early writers that there is rather more likelihood of obtaining a living child in patients who develop diabetes during pregnancy than in those who were diabetic before conception. This is probably because diabetes complicating pregnancy is frequently mild and, the disease being of short duration, the mother is likely to be in good condition.

II. *Excessive size of the foetus.* It has long been known that the foetuses of diabetics tend to show excessive skeletal development and to be well supplied with subcutaneous fat. Yet, in spite of its manifest importance, this phenomenon has received little attention during recent years and is not alluded to in most modern text-books. But it is no exaggeration to state that the birth of a child of excessive size always suggests the advisability of investigating the mother for diabetes. In 18 per cent. of the collected cases in which the weight is mentioned the child weighed 10 lb. or more, the largest being a giant foetus of over 7 kg. (49). Seven children in the London Hospital series weighed over 10 lb., while a previous pregnancy of Case No. 31 was said to have resulted in a stillborn child of 15 lb. This over-development is a not uncommon source of danger to the foetus and may cause its death from trauma sustained during difficult labour (57, 90).

Why the foetus should be large in diabetes is a matter for conjecture, but it is tempting to correlate its abnormal amount of adipose tissue with maternal hyperglycaemia. Thus the child tends to be fat, especially when the maternal disease has not been well controlled during pregnancy. In these circumstances the foetus is presented with a rich supply of glucose from the maternal blood-stream, glucose being readily diffusible across the placenta from mother to child (97). The excess sugar is presumably partly converted into fat and stored. It may be noted that high blood-sugar values have been found in the umbilical cord in diabetics (Ambard et al. = 0·242 per cent.). In six of the Hospital cases the blood-sugar in the umbilical vein, estimated immediately after birth, varied from 0·08 to 0·134 per cent., and was in each instance slightly lower than in the mother. The ease with which glucose passes through the placenta was well shown in Case No. 29. This patient was purposely kept hyperglycaemic during labour by the oral administration of glucose. Immediately after delivery the concentration of sugar both in the maternal capillary blood and in the umbilical vein was 0·25 per cent.

III. *Hydramnios.* Before insulin, hydramnios was said to complicate 27 per cent. of cases (18, 64) and to have been a not infrequent cause of premature labour in the diabetic. Its incidence has diminished (11 per cent.) and it does not now appear to be of great significance, although Voron and Gaucherard were forced to puncture the membranes in their case because of symptoms of maternal distress. Hydramnios only occurs if the diabetes is neglected, and has been known to disappear on instituting treatment with insulin (52, 54). There was only one example of hydramnios in the Hospital cases, and this was in a woman who broke treatment continually. The presence of sugar, possibly derived from the foetal urine, has been reported several times in the liquor amnii of diabetics, although it was not discovered in six consecutive cases in the Hospital series. Although the explanation is largely speculative the sugar content of the liquor in diabetes is possibly the cause of the hydramnios, the raised osmotic tension in the amniotic cavity

bringing about an inflow of fluid from the surrounding tissues. A further possibility is that the excess of liquor results from intra-uterine foetal diuresis consequent upon foetal hyperglycaemia (56).

IV. *Congenital abnormalities.* Since Lecorché reported that two of his diabetics bore hydrocephalic children, it has been stated, although hitherto with little evidence, that congenital anomalies are common in the foetuses of diabetics (94, 110). Congenital defects are mentioned in 3 per cent. of the collected cases and include a case of meningocele resulting in operative cure (81), a case of bilateral double ureter and pelvis (35), and two instances of congenital morbus cordis (73). It is of interest that Rosenberg in pre-insulin days also recorded that the child of a diabetic died with congenital heart disease and that the infant of Case No. 5 of the London Hospital series apparently succumbed from this condition. A previous pregnancy of Case No. 28 resulted in the birth of a monster. Although the number of cases is too small to allow definite conclusions to be drawn, there would certainly seem to be an unusual tendency for the children of diabetics to show congenital abnormalities, and that these constitute a small but quite definite factor in the foetal mortality.[3]

V. *Foetal hypoglycaemia.* Hypertrophy of the islands of Langerhans of foetuses born of diabetics has been observed on five occasions (26, 29, 35, 73, 110) and is probably to be regarded as a compensatory reaction of the foetal pancreas in response to an excess of glucose in the placental circulation. Thus, in each case in which this histological change was found, the maternal blood-sugar had not been well controlled during pregnancy. As the hypertrophic islands would be expected to secrete an abnormally large amount of insulin, it has been suggested that the child of a badly treated diabetic, if born alive, is in danger of succumbing from hypoglycaemia developing after birth. In Gray and Freemster's case the child's blood-sugar, three days after birth, was 0·067 per cent. The child died on the fourth day with a 'peculiar pasty colour', but in addition to hypertrophic islands of Langerhans autopsy revealed other lesions sufficient to have caused death. Although the blood-sugar in the child cited by Nevinny and Schretter was 0·052 per cent. at birth, it later rose to 0·172 per cent., and death occurred from congenital morbus cordis. There is no evidence in the other cases that death was due to hypoglycaemia. It should be pointed out that the low blood-sugars quoted above are within normal limits for the new-born (96). In Case No. 29 the child's blood-sugar ten hours after birth was only 0·045 per cent., yet no unusual symptoms were observed. Although in the diabetic foetal death from hypoglycaemia originating in this way seems very possible, definite proof of its occurrence is thus lacking, and further observations are necessary. The foetal pancreas in Cases Nos. 9 and 22 showed hypertrophic changes in the islands of Langerhans, but a report upon these is deferred pending the collection of other material.

[3] Since this paper was written a post-mortem upon the stillborn child of a diabetic revealed a large diaphragmatic hernia.

There is also the possibility of the intra-uterine death of the foetus from hypoglycaemia during maternal insulin reactions (56), but again there is no definite evidence that this has occurred. It is interesting that Case No. 32 stated that the foetal movements became very violent when she was hypoglycaemic. Lambie's patient, however, noticed a cessation of foetal movements under like circumstances.

VI. *'Congenital' diabetes.* According to Joslin an hereditary and familial tendency to diabetes is present in 24·6 per cent. of all diabetics and in a slightly greater percentage of diabetic children. It remains to be discussed whether there is any evidence that the children of women who are diabetic during pregnancy may be born with the disease or whether they are specially prone to develop it. Wolff alleged that 10 per cent. of living babies born of diabetics contracted diabetes shortly after birth and succumbed within a few years, apparently basing his opinion upon an earlier paper by Offergeld. Reference to the cases collected by the latter author, however, make it clear that there was no justification for Wolff's statement. With the possible exception of a child which was said to have died at twenty-one months, with hydrocephalus, thirst, and polyuria, it is very doubtful that any of the children in Offergeld's series had or developed diabetes. Several showed glycosuria at birth, but this alone is insufficient evidence of diabetes, for the foetus may pass sugar in the urine after birth if its blood-sugar was raised *in utero* owing to maternal hyperglycaemia. The following are instances of alleged congenital diabetes. In Morrison's case a new-born child was said to have died from diabetes, and the diabetic mother also succumbed. No further details are given. Ambard et al. described an intra- and inter-lobar fibrosis of the pancreas in the foetus of a diabetic. The child's urine contained 1·2 per cent. of sugar, and death occurred in twenty-three hours, but the islands of Langerhans were said to be normal. Feldman's case is even less convincing. In addition to showing hypertrophy, the islands of the foetal pancreas were oedematous, and an interstitial pancreatitis was described. *Post mortem*, the foetal urine was found to contain sugar. In view of the well-known difficulty in interpreting changes in the pancreas, it would be unwise to assume congenital diabetes in either of these cases. Moreover, it is not in favour of diabetes that the grossest lesions were stated to be in the glandular portion of the pancreas and not in the islands. Both Naunyn and Joslin wrote that they had never seen a congenital diabetic, and the former recognized no authentic case in the literature.

The offspring of a diabetic mother may, of course, later develop diabetes because of the hereditary factor, but there is nothing to suggest that this is more likely to occur if the mother is diabetic during her pregnancy than if she contracts the disease at some future date. Suspicion attaches to the child of Case No. 21. From the age of twenty-one months glucose has been present in the urine from time to time in amounts varying from 0·5 to 1·4 per cent. Sugar-tolerance tests have so far proved normal, and the cause of the glycosuria remains in doubt. One other, Case No. 17, has shown an

occasional trace of sugar since it was ten months old, although the blood-sugar is normal. Both these childen appear healthy, but are being carefully watched. The other children are all perfectly normal and show no signs of diabetes. Two were found to have very slight glycosuria at birth, but subsequent specimens of urine were sugar-free.

The Significance of the Glycosurias of Pregnancy

Sugar in some form has been found on routine examination of the urine in from 4 to 13·6 per cent. of pregnant women (53, 86, 116). It is quite generally held that the glycosuria is usually due to a low threshold which, as has been emphasized, is common during pregnancy. Thus, in certain gravid women, although the blood-sugar response to the ingestion of glucose is normal, sugar is found in the urine during the sugar-tolerance test or after an ordinary meal because the threshold is low. Apart from the excretion of sugar, carbohydrate metabolism appears to be undisturbed. This is the only variety of glycosuria of pregnancy to which the term 'renal' should be applied. A large proportion of pregnant women who excrete sugar in the urine may, however, be demonstrated to have a lowered assimilation limit for carbohydrate, quite apart from diabetes mellitus. The fasting blood-sugar is either normal or slightly raised, but these individuals, sometimes quite early in pregnancy, show a delay in the fall of the blood-sugar after the oral administration of glucose, a flattened curve resulting. According to some authors it is the prolongation of the curve rather than the height to which the blood-sugar rises which is abnormal (53, 109). Others report definite hyperglycaemia, the character of the curve approximating to that of true diabetes (43, 86, 93). Pillman-Williams and Wills found hyperglycaemia after 100 grm. of oral glucose in 80 per cent. of pregnant women who had symptomless glycosuria upon an ordinary diet, and they concluded that the renal threshold was probably also lowered in all their cases. In the writer's experience, hyperglycaemia during pregnancy in non-diabetics is comparatively rare, but the 'plateau' type of curve is not uncommon and is practically always associated with a low renal threshold. In such cases the glycosuria is due to the latter and not to a hyperglycaemia. Because patients with these anomalous curves tend to excrete sugar after meals, the condition has been almost universally referred to as 'alimentary glycosuria' of pregnancy, but this term is misleading and has led to considerable confusion, for also in ordinary renal glycosuria and in true diabetes sugar may be present in the urine after the taking of food. For the sake of clarity it will be here referred to as 'impaired carbohydrate tolerance of pregnancy'. It is said that the curve returns to normal after delivery, although the work of Williams and Wills suggests that this is not always the case. It has also been suggested that this disturbance of metabolism may reappear during successive pregnancies, ultimately leading to true diabetes (56, 93). While there is some

evidence to support this, the writer is unaware of any instance in which the transmission into diabetes has been proved by blood-sugar estimations. The condition is sometimes accompanied by diabetic symptoms and, it is alleged, although the evidence for this is inconclusive, by over-development of the foetus or by hydramnios. The exact significance of impaired carbohydrate tolerance of pregnancy is at present unknown, and further work on the subject is necessary. It would seem rational to regard it as a 'pre-diabetic' condition, and as one that might be expected to develop into true diabetes in patients predisposed to the disease by heredity, adiposity, or possibly by repeated pregnancies.

Some observers hold that a woman may be 'diabetic' during pregnancy only, making a complete recovery after labour (103, 110), but the writer has never seen a permanent return to normal metabolism in any patient who showed a diabetic sugar-tolerance curve when pregnant. Cases in which the diabetes was said to disappear after childbirth were probably not observed over a sufficiently lengthy period. The tolerance of the diabetic may improve greatly after delivery, and, with the rise of the threshold, glycosuria frequently ceases. Yet, if the patient be placed upon an unlimited diet, the sugar-tolerance curve will sooner or later show the persistence of the diabetic condition, although, as with any mild diabetic after a course of treatment, the curve may be normal for a considerable time.

Records show that it is not unusual for patients to develop diabetes during the course of a pregnancy. This occurrence is, indeed, sufficiently frequent to warrant the statement that pregnancy is one of the aetiological factors of the disease. That such individuals are sometimes 'predisposed' is suggested by the fact that it is not uncommon to obtain from them a family history of diabetes.

From what has been said it will be gathered that pregnancy may be accompanied by a disturbance of carbohydrate metabolism, which in some individuals may be merely temporary and in others may precipitate the onset of permanent diabetes. As elsewhere explained, pregnancy may also render a pre-existing diabetes temporarily more severe. The reader is referred to other papers for the many explanations which have been advanced to account for these phenomena (27, 56, 73).

Diagnosis

In discussing the differential diagnosis, the following conditions which are associated with the excretion of sugar in the urine during pregnancy must be considered:

1. Glycosuria: (*a*) Renal glycosuria; (*b*) Impaired carbohydrate tolerance of pregnancy ('alimentary glycosuria'); (*c*) Diabetes mellitus.
2. Lactosuria.

I. *Glycosuria.* There has in the past been a tendency to assume too readily that a positive reduction of Fehling's solution obtained during

pregnancy is harmless and may be ignored. Such an assumption is dangerous, for it has frequently led to the overlooking of the milder degrees of diabetes with disastrous results to the pregnancy. Undiagnosed diabetes is undoubtedly responsible for more stillbirths than has been suspected, and the opinion is therefore here expressed that glycosuria in the pregnant woman, like albuminuria, should always be investigated. Difficulty is likely to be encountered only in mild cases of diabetes when symptoms are lacking or indefinite, especially when the onset of the disease is during pregnancy, and only the more important points in connexion with the diagnosis of this type of case will be dealt with here.

Regarding the clinical history, it must be remembered that mild thirst, polyuria, and especially pruritus vulvae, are not uncommon in the non-diabetic glycosurias, and, indeed, any pregnant woman may complain of them. A history of definite diabetic symptoms during the latter months of previous pregnancies, especially if these resulted in heavy children or in stillbirths, is strongly in favour of diabetes. Diabetics not uncommonly bear a series of large children and it is interesting to note that these may precede the onset of diabetic symptoms (17, 60). Similarly, the discovery of over-development of the child or of hydramnios on physical examination is very suggestive of diabetes but does not entirely exclude impaired carbohydrate tolerance of pregnancy. As distinct from diabetes mellitus, in the non-diabetic glycosurias the amount of sugar in the urine is usually small, under 1 per cent., and the glycosuria tends to be intermittent, although when the threshold is very low sugar may be excreted continuously. Ketonuria is generally absent.

The sugar-tolerance test, which is of far greater value than single blood-sugar estimations in distinguishing between the glycosurias of pregnancy, should always be carried out whenever there is the slightest suspicion of diabetes. It is essential that the patient does not receive a diet restricted in carbohydrate for some days before the test is performed, for, if this precaution is not observed, a mild diabetic may give a normal blood-sugar response leading to an error in diagnosis. The curves obtained in simple renal glycosuria and in diabetes are too well known to need description. In impaired carbohydrate tolerance of pregnancy, the blood-sugar seldom rises as high as in true diabetes, rarely reaching 0·2 per cent., and the fasting blood-sugar is almost invariably below 0·12 per cent. Border-line cases, difficult to distinguish from true diabetes, are sometimes encountered, and should be regarded as suffering from the more serious condition.

II. *Lactosuria.* According to Cron, lactosuria occurs in 3·5 per cent. of women during the last few weeks of pregnancy. Its real incidence is probably much higher, for Commandeur and Porchet by repeated search found it in thirty consecutive patients either in late pregnancy or in the early puerperium. It not uncommonly alternates with or accompanies glucose in any of the varieties of glycosuria. Lactosuria may be suspected when, in the absence of diabetic symptoms, the urine contains a small quantity of

sugar, usually under 1 per cent., as term is approached. Very occasionally it is found quite early in pregnancy. Lactose may be recognized by its inability to ferment with yeast, or by its osazone crystals, shaped like chrysanthemums.

Treatment

With certain modifications rendered necessary by the special conditions obtaining during pregnancy, the treatment is similar to that of any diabetic. Because of the importance of rigid control of the disease, the patient should, if possible, enter hospital at the commencement of treatment. To ensure success, careful antenatal supervision throughout the gestation period and close co-operation between physician and obstetrician are essential, and the patient should be informed of the importance of complying with the instructions laid down for her.

Foci of infection must be suitably dealt with, for these are harmful to the disease, and for a similar reason the patient should be warned against contact with acute infections of any kind. During pregnancy, particular attention should be given to the teeth, and the possibility of infection of the urinary tract with the colon bacillus should be borne in mind.

Diet and insulin. No increase in the quantity of food usually taken by the diabetic is necessary, for it has been shown that the caloric requirements of the individual are only about 4 per cent. greater during pregnancy (16). A diet which supplies from 25 to 30 calories per kg. body-weight, according to the nutritional state and activity of the subject, is ample to meet the demands of pregnancy. The amount of protein allowed should be from 1 to $1\frac{1}{3}$ grm. per kg., and, for reasons given, the diet should be relatively rich in carbohydrate and should contain only a moderate amount of fat. The proportion of carbohydrate to fat should be such that the F A : G ratio is low, preferably about 1 : 1·5. To fulfil these requirements, the diet will contain on the average from 120 to 140 grm. of carbohydrate and from 90 to 110 grm. of fat daily. Such a diet has been found very satisfactory, and with insulin, if necessary, forms a valuable safeguard against ketosis. Moreover, the relatively high carbohydrate content allows the inclusion of plenty of milk, e.g. $1\frac{1}{2}$ pints daily, to supply the calcium needs of the mother. As with any pregnant woman, especially during the winter months, it is advisable to prescribe cod-liver oil or some other preparation furnishing vitamins A and D.

During treatment an effort should be made to keep the blood-sugar below 0·16 per cent., insulin being employed to effect this if necessary. It is here that the two-hourly blood-sugar curves, elsewhere described, are of valuable assistance. To prevent the intra-uterine death of the foetus or its excessive development, the level of the blood-sugar must be carefully watched throughout pregnancy, especially during the latter months. In addition to the fortnightly examination of the urine and the blood-sugar, the patient should be admitted to hospital for a short period of observation and a

repetition of the two-hourly blood-sugar curve every two months. The dose of insulin will often have to be raised during the second half of gestation, and owing to the frequency of lowering of the renal threshold, the blood-sugar is a better guide to the amount of insulin required than the state of the urine. When the threshold is very low, it is impossible to keep the urine entirely free from sugar, and attempts to do so provoke hypoglycaemia.

Should diabetic coma occur, the chances of survival of the child are slight. There is no advantage in emptying the uterus, and such a procedure is highly dangerous. It is far better to await the natural onset of labour while carrying out the usual treatment of coma.

In cases of impaired carbohydrate tolerance of pregnancy such careful observation is unnecessary, and usually moderate restriction of carbohydrate is sufficient to control the blood-sugar, but insulin should be used if there is hydramnios or if the child shows signs of over-development. As stated, border-line cases should be regarded as diabetics and treated accordingly. Simple renal glycosuria requires no treatment, but a lotion may be employed to relieve the pruritus vulvae which is sometimes severe.

Childbirth and the puerperium. Until the last few years it has been the practice at this hospital to effect delivery by Caesarean section under spinal anaesthesia, on the grounds that the dangers of a possibly difficult labour or an emergency general anaesthetic are thus avoided. Moreover, if thought to be indicated, sterilization can be carried out at the same operation. Recent experience, however, has abundantly proved that with proper management even the severe diabetic can be safely brought through labour, and it is now the custom to allow normal delivery, provided antenatal supervision reveals no disproportion between the size of foetus and pelvis or malpresentation likely to cause trouble. Excessive size of the child is now the chief indication for Caesarean section in the diabetic, and delivery by this method would have been the best treatment in Case No. 31. During labour, milk, orange juice, and sugar in amounts corresponding to the 'glucose value' of the patient's diet should be given, and in the severe cases an extra dose or two of insulin, according to the duration of labour, should be injected. By this means ketosis is avoided and the patient is in better state to withstand anaesthesia should this prove necessary. Similar precautions should be taken on the day of Caesarean section. If for any reason a general anaesthetic is indicated for this operation, gas and oxygen is undoubtedly the best. Chloroform and ether, especially the former, should be avoided.

Assuming the possibility of spontaneous hypoglycaemia in the child after birth, Wilder and Parsons recommend its feeding with other breast milk as soon as possible instead of waiting as is customary until the mother can herself provide nourishment. On similar grounds, it would be a rational procedure to give the child a subcutaneous injection of glucose should it show signs of morbidity. This was tried unsuccessfully in Case No. 9.

During the puerperium a close watch should be kept for symptoms of maternal hypoglycaemia necessitating a reduction in the dose of insulin, for there is a danger of hypoglycaemic coma at this time. Puerperal infection, said to be common in pre-insulin days, is now no longer to be especially feared. One or two days after delivery the mother may return to her usual diet.

Lactation. Lactation was tried in eight cases with rather variable results. Three women, all mild diabetics, were able to nurse their children for the usual length of time. In 4 other cases the milk became scanty and breast-feeding had to be curtailed. In the eighth case a mammary abscess proved a contra-indication to nursing. It was found that if the diabetes was not controlled, the flow of milk considerably diminished. Thus in Case No. 33, who broke treatment and whose blood-sugar was high, lactation was unsuccessful, and in Case No. 31 the child had to be weaned at the fourth month when an attack of influenza in the mother precipitated glycosuria. In 7 cases samples of milk were analysed and were found to contain normal amounts of lactose, protein, and fat. Successful lactation in diabetics has been reported by some authors (68, 81, 115), but McIlroy et al. found defective secretion in all their cases. Wilder and Parsons suggest that insulin may play no part in the formation of lactose in the breast tissue, and if this is true, suckling would not appear to be contra-indicated in the diabetic. Certainly there is no evidence from clinical observation that it is in any way harmful. It seems very likely that the restricted diet taken by the diabetic is responsible for some of the failures. Assuming that 900 c.c. of milk are secreted during the 24 hours when lactation is properly established, there is a daily loss to the mother of from five to six hundred calories which can only be met by increasing the food intake. It is suggested that, provided the diabetes is under control, lactation should always be tried. In the milder cases the diet may be increased to meet the demands of suckling, insulin being used to control glycosuria if necessary, but it is doubtful whether this step is justified in severe diabetics. If the child does not gain weight normally, supplementary feeding may be used.

Sterilization. There has been much controversy over the question of sterilization of the diabetic. Obviously each case must be judged individually. In making the decision, due consideration should be given to the home conditions, the number of children the patient already possesses, and to whether or not she wishes for more. If another child is desired, there is no reason why it should not be allowed, provided the patient is able and willing to remain under adequate supervision, for it has been shown that pregnancy, if properly managed, is not harmful to the diabetic. A patient whose mentality is such that her co-operation during possible future pregnancies would seem to be unlikely should be sterilized. The operation should also be performed upon severe diabetics when the disease has proved difficult to control during the gravid state. In such circumstances the fate of the child is always uncertain, and further child-bearing is best avoided.

As stated, there is no evidence that the child of a woman who is diabetic during her pregnancy is specially liable to develop the disease, and hence there can be no plea for sterilization on eugenic grounds. If pregnancy is to be prevented for fear that the children may later develop diabetes, then child-bearing in the patient's non-diabetic blood-relations should also be prohibited, for they may equally well transmit the diabetic taint to their offspring.

When indicated, sterilization may be carried out under spinal anaesthesia a few weeks after labour, or it may be performed at the time of operation when delivery is by Caesarean section.

Summary and Conclusions

1. The use of insulin has considerably lowered the maternal mortality of diabetics during pregnancy and the puerperium, but has led to no reduction in the foetal mortality.

2. Insulin exerts a beneficial effect upon the fertility of the diabetic.

3. Diabetics usually lose tolerance during the latter months of pregnancy.

4. Although uncommon, an increase in tolerance may occur in the last half of gestation. There is no good evidence that this is due to the transference of insulin from foetus to mother.

5. A gain in tolerance may be frequently observed after childbirth, the metabolic state of the patient often returning to that prior to conception. Hypoglycaemia during the puerperium is almost invariable in patients receiving insulin and may lead to hypoglycaemic coma. It has been shown that lactation is not the chief cause of this hypoglycaemia.

6. With adequate treatment, pregnancy is not harmful to the diabetic.

7. In the diabetic the renal threshold for glucose is frequently low during pregnancy, rising again after delivery. The threshold may, however, be above normal during pregnancy.

8. Ketonuria is common in the pregnant diabetic, and there is a special liability to diabetic coma in the badly treated case. In addition to insulin a diet relatively high in carbohydrate and low in fat is usually necessary to prevent ketonuria. The ketonuria disappears spontaneously after delivery.

9. The most important cause of foetal death is poor control of the maternal disease, particularly in the last months of gestation. Other causes are over-development of the foetus and congenital abnormalities. Hydramnios may be an occasional source of danger to the child. The occurrence of fatal hypoglycaemia in the child after birth associated with hypertrophy of its islands of Langerhans has not yet been proved.

10. No evidence of congenital diabetes has been found. The child of a woman who is diabetic during her pregnancy is not specially liable to develop the disease.

11. As diabetes may commence during gestation, it is suggested that every pregnant woman whose urine contains sugar should be investigated as a possible diabetic.

12. During treatment constant supervision and rigid control of the blood-sugar are of great importance. Only thus can a living child be obtained with reasonable certainty.

13. Diabetics can now be safely brought through labour, but Caesarean section may be necessary when the foetus is of excessive size.

14. Breast-feeding, although sometimes unsuccessful, should always be tried, for it is not harmful to the disease. Good control of the diabetes and an adequate diet are necessary for the maintenance of lactation.

15. Certain indications for the sterilization of the patient have been mentioned. Further pregnancies may be allowed in suitable cases if circumstances are favourable.

For permission to publish the cases I am indebted to numerous members of the Honorary Staff of the London Hospital, particularly to my chief, Dr. Leyton, under whose care the majority of the patients were admitted, and whom it is a great pleasure to thank for valuable suggestions in the writing of this paper. My best thanks are also due to Miss Rose Simmonds, the Hospital dietitian, for her skilful arrangement of the various diets.

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Appendix I

Case no.	Before pregnancy. Calories per diem.	Blood-sugar mg. %.	Insulin: units per diem.	During pregnancy. Weeks.	Calories per diem.	Blood-sugar mg. %.	Insulin: units per diem.	Weeks.	Calories per diem.	Blood-sugar mg. %.	Insulin: units per diem.	Puerperal Hypoglycaemia.	After pregnancy. Interval.	Calories per diem.	Blood-sugar mg. %.	Insulin: units per diem.	Interval.	Calories per diem.	Blood-sugar mg. %.	Insulin: units per diem.
5	1465	117	15	21	1345	—	15	35	1130	100	52	Nil	1 mo.	1650	*125*	30	5 yrs.	1101	200	52
6	1345	120	30	13	1345	111	30	38	1345	130	30	+	1 yr.	1526	—	30	5 yrs.	1680	100	14
9	1264	133	—	23	1264	101	20	36	600	400	175	Nil	3 wks.	1243	*143*	25	1 yr.	1234	—	30
1st pregnancy 2nd pregnancy	1243	—	40	17	1243	140	40	30	1667	108	90	+ (Coma)	4 mos.	1703	130	50	18 mos.	1699	90	70
10 1st pregnancy 2nd pregnancy	1260	*110*	30	18	1260	—	20	34	1814	77	10	Nil	15 mos.	Unlimited	102	—	3 yrs.	Unlimited	201	—
11	—	—	—	12	1105	100	—	31	1670	*135*	30	+	6 wks.	1625	—	10	4 yrs.	1670	298	25
13	1321	—	50	12	1605	242	40	34	1601	—	55	+ (Coma)	3 wks.	1556	210	50	3½ yrs.	1556	—	40
14	1586	143	—	15	1586	—	—	32	1586	*154*	—	—	5 mos.	1559	*286*	—	18 mos.	—	Died	—
15	1452	70	70	17	1362	180	40	39	1638	115	70	+ (Coma)	8 mos.	1669	130	60	3 yrs.	1628	74	72
16	—	—	—	10	1768	*143*	20	35	1426	95	70	+	6 mos.	1620	100	40	3 yrs.	1785	110	80
21	1110	211	—	13	Unlimited	142	—	30	1760	60	30	+	7 mos.	1760	160	24	3 yrs.	1760	120	32
22	1533	—	40	13	1533	*180*	40	26	1764	40	120	+	6 mos.	1772	131	50	2½ yrs.	1772	*86*	55
23	1470	*154*	20	6	1470	—	30	36	1779	72	105	+	3 mos.	1806	70	40	2 yrs.	1602	95	60
25	?	266	—	14	1760	125	—	31	1649	100	50	+	3 mos.	1617	97	50	18 mos.	1617	*220*	60
26	1808	132	50	14	1690	71	50	37	1773	252	50	+	4 mos.	1773	—	35	17 mos.	1773	137	60
29	1350	*160*	—	15	1580	78	—	35	1580	86	—	—	6 mos.	Unlimited	114	—	11 mos.	1090	200	—
31	1501	*266*	40	15	1501	122	40	35	1820	80	80	+	10 dys.	1807	133	68	6 mos.	1807	76	60
33	1515	282	80	18	1515	—	40	34	1669	95	120	+	6 wks.	1938	102	80	3 mos.	1832	201	80

This table represents changes in the metabolism of diabetics during pregnancy and after delivery. The blood-sugars are fasting values, with the exception of those shown in italics which were taken 1–2 hours after a meal.

APPENDIX II. *London Hospital Cases*

Case no.	Mother's age. Yrs.	Previous pregnancies.	Apparent onset of diabetes. Before pregnancy. Yrs.	Apparent onset of diabetes. During pregnancy. Mos.	Degree of diabetes.	Apparent control of diabetes.	Insulin used.	Child. Mother.	Child.	Duration of pregnancy.	Child's weight. lb.	Child's weight. oz.	Remarks.
Case 1	36	8	½	—	Mild	Poor	—	Lived	Dead	7 mos.	?	?	Coma during labour which was induced at 7th month. Sterilized later.
Case 2 (i)	37	4	10	—	Mild	Poor	—	—	Lived	Term	?	?	Eclampsia on day after delivery.
(2 pregnancies) (ii)	—	—	—	—	—	Poor	—	Lived	Therapeutic abortion	7 wks.	—	—	Abortion performed because of diabetes and previous eclampsia.
Case 3	38	5	2	—	Moderate	Poor	—	Lived	Therapeutic abortion	4 mos.	—	—	Insulin therapy commenced after abortion.
Case 4	31	0	—	7	Mild	Poor	—	Lived	Lived	8 mos.	7	0	3 weeks' treatment only. Insulin commenced after labour.
Case 5	42	7	2	—	Moderate	Poor	Throughout	Lived	Died in 3 mos.	Term	6	3	Ketosis during pregnancy. Caesarean section under spinal anaesthesia. Child died with ? congenital morbus cordis.
Case 6	24	0	6	—	Moderate	Good	Throughout	Lived	Lived	Term	6	9	Caesarean section under general anaesthesia.
Case 7	32	5	2½	—	Severe	Poor	Throughout	Lived	Dead	Term	10	12	Diet broken during pregnancy. Hydramnios. Caesarean section under spinal and gas and oxygen anaesthesia. Mother died 4 years later with peritonitis. Family history of diabetes.

Case 8		31	3	3	—	Moderate	Good	Throughout	Lived	Hysterotomy	3 mos.	—	—	Foetus removed by hysterotomy. Sterilization under spinal and general anaesthesia.
Case 9 (2 pregnancies)	(i)	23	0	½	—	Severe	Poor	Irregularly	—	Dead	8 mos.	3	0	Ketosis during pregnancy. In coma just before labour as did not take insulin. Juvenile myxoedema.
	(ii)	—	—	—	—	—	Poor	Throughout	Lived	Died in few mins.	Term	9	9	Diabetes difficult to control. Ketosis during pregnancy. Ceasarean section and sterilization under spinal anaesthesia. Mild puerperal pyrexia.
Case 10 (2 pregnancies)	(i)	32	2	—	4	Mild	Good after 7 mos.	At 7 mos.	—	Lived	Term	9	13	Ketosis during pregnancy. Family history of diabetes.
	(ii)	—	—	—	—	—	Good	Throughout	Lived	Lived	Term	11	0	—
Case 11		29	0	½	—	Moderate	Good	At 7 mos.	Lived	Lived	Term	7	0	Ketosis during pregnancy. Caesarean section and sterilization under spinal anaesthesia.
Case 12 (2 pregnancies	(i)	38	7	1½	—	Moderate	Poor	—	—	Dead	8 mos.	11	0	Became severe diabetic after this pregnancy.
	(ii)	—	—	—	—	—	Poor	Throughout	Lived	Abortion	9 wks.	—	—	Abortion, following severe cold, completed under spinal anaesthesia.
Case 13		24	4	1	—	Moderate	Good	Throughout	Lived	Lived	Term	?	?	Delivery out of hospital.
Case 14		—	8	4/12	—	Moderate	Good	—	Lived	Lived	Term	10	11	Broke treatment after delivery. Died 18 months later from phthisis and coma.
Case 15		26	0	2½	—	Severe	Poor	Throughout	Lived	Lived	Term	7	1	Diabetes difficult to control. Ketosis during pregnancy. Caesarean section and sterilization under spinal anaesthesia. Family history of diabetes.
Case 16		20	1	1½	—	Moderate	Good	Throughout	Lived	Lived	Term	11	0	Ketosis during pregnancy. Caesarean section and sterilization under general anaesthesia.

Appendix II (*continued*)

Case no.	Mother's age. Yrs.	Previous pregnancies.	Apparent onset of diabetes. Before pregnancy. Yrs.	Apparent onset of diabetes. During pregnancy. Mos.	Degree of diabetes.	Apparent control of diabetes.	Insulin used.	Child. Mother.	Child.	Duration of pregnancy.	Child's weight. lb.	Child's weight. oz.	Remarks.
Case 17	39	2	—	6	Mild	Untreated	At 8 mos.	Lived	Dead	8 mos.	7	5	Admitted in coma. Labour induced after recovery.
Case 18	28	0	—	6	Moderate	Poor	At 7 mos.	Lived	Lived	Term	9	12	Caesarean section and sterilization under spinal anaesthesia. Family history of diabetes.
Case 19	28	2	—	2	Mild	Untreated	—	Lived	Dead	8 mos.	?	?	Family history of diabetes. Now again pregnant.
Case 20	23	4	—	6	Mild	Poor	Last 2 wks.	Lived	Lived	Term	10	2	2 weeks' treatment only. Ketosis during pregnancy. Caesarean section and sterilization. Spinal anaesthesia. Child did not thrive on breast milk.
Case 21	35	3	½	—	Moderate	Good	At 3 mos.	Lived	Lived	Term	5	11	Caesarean section and sterilization. Spinal anaesthesia.
Case 22	32	0	2½	—	Severe	Poor	Throughout	Lived	Died in 3 hrs.	Term	6	0	Diabetes very difficult to control. Ketosis during pregnancy. Caesarean section and sterilization. Spinal anaesthesia. Family history of diabetes.
Case 23	31	2	2	—	Severe	Good	Throughout	Lived	Lived	Term	9	12	Ketosis and pyelitis during pregnancy. Caesarean section and sterilization under spinal anaesthesia.

Case 24	27	1	—	5	Moderate	Good	At 5 mos.	Lived	Lived	Term	8	13	Ketosis during pregnancy. Sterilization under spinal anaesthesia later.
Case 25	39	1	3½	—	Moderate	Good	At 6 mos.	Lived	Lived	Term	7	12	Ketosis during pregnancy. Caesarean section and sterilization. Also hysterectomy for fibroids. Spinal anaesthesia. Family history of diabetes.
Case 26	31	3	1½*	—	Moderate	Good until 8 mos.	Throughout	Lived	Dead	8 mos.	8	14	Influenza at 8 months. Child died *in utero*. Sterilized later.
Case 27	30	3	—	2	Mild	Good after 7 mos.	—	Lived	Lived	Term	7	6	Untreated until 7th month. Nursed baby 8 months. Family history of diabetes.
Case 28	39	5	1½*	—	Mild	Good after 7 mos.	At 7 mos.	Lived	Lived	Term	9	11	Ketosis during pregnancy. Nursed baby 8 months. Previous child a monster.
Case 29	40	0	4/12	—	Mild	Good	—	Lived	Lived	Term	7	13	Ketosis during pregnancy. Nursed baby 6 months.
Case 30	44	9	1½	—	Mild	Good after 7 mos.	At 7 mos.	Lived	Lived Twins	Term	6 5	0 8	Breast abscess interfered with lactation. Previous history of heavy children.
Case 31	32	2	7	—	Severe	Good after 5 mos.	Throughout	Lived	Lived	8 mos.	10	11	Ketosis during pregnancy. Difficult forceps delivery under gas and oxygen. Nursed baby 4 months. A previous child weighed 15 lb.
Case 32	45	5	2½	—	Mild	Good after 7 mos.	—	Lived	Lived	Term	7	15	Fed child 3 months. Previous history of heavy children. Family history of diabetes.
Case 33	42	6	3	—	Severe	Poor	Throughout	Lived	Died in 3 mos.	8 mos.	4	15	Did not keep to diet. Lactation unsuccessful. Child died aged 3 months with pneumonia.

37 pregnancies in 33 diabetics { Maternal mortality during pregnancy or puerperium = nil.
Foetal mortality = 40·5 %.

* Diabetes apparently arose during a previous pregnancy.

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THE EFFECT OF YEAST AND WHEAT EMBRYO IN ANAEMIAS[1]

1. MARMITE, YESTAMIN, AND BEMAX IN MEGALOCYTIC AND NUTRITIONAL HYPOCHROMIC ANAEMIAS

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The present work originated in 1930, when, during the administration of wheat germ as a source of vitamin B_1 to a patient with pernicious anaemia and subacute combined degeneration of the cord, a reticulocyte response was observed (32). The substance was given to determine a possible effect upon the neurological condition (see Gildea, Kattwinkel, and Castle (12)), and the rise of reticulocytes was quite unexpected.

Since that time observations have been carried out to determine the effect of large doses of wheat germ and of yeast preparations in certain forms of anaemia. The results will be discussed under three headings, according to the types of anaemia studied. 1. *Nutritional Hypochromic Anaemias.* 2. *Atypical Pernicious Anaemia without Achlorhydria.* Including an unusual case of Dysphagia with Anaemia (Pernicious). 3. *Addisonian Pernicious Anaemia.*

Methods

While under observation in hospital the patients received a diet containing no liver, kidney, brain, or other material potent in pernicious anaemia apart from the substance to be assayed. With two exceptions, noted in the respective case reports, the diet during the test periods in hospital contained no meat. Wheat germ in the form of Bemax was administered with milk, milk puddings, or stewed fruit, an attempt being made to maintain a dosage of 120 or 240 grm. daily. Yestamin, which is dried brewer's yeast, was given in a similar manner, but the average daily amount consumed never exceeded 48 grm. Marmite, an extract of autolysed brewer's yeast, was administered chiefly in hot water as a drink, but also in sandwiches. The Marmite was measured by weight and not by tea- or tablespoonfuls, and in most cases it was possible to maintain a dosage of

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120 grm. daily. In view of digestive disturbances sometimes caused by the administration of such large amounts, the Marmite was subsequently fractionated by 65 per cent. alcoholic extraction.

Method of preparing 65 per cent. alcoholic extract of Marmite. A weighed quantity of Marmite is mixed with enough water to make a thin paste. Sufficient absolute alcohol is now added in quantities sufficient to render the whole solution 65 per cent. with regard to alcohol. The liquid is shaken and left overnight, after which it is filtered under pressure. The filtrate is subsequently heated on a water-bath to evaporate the alcohol. During the process the temperature of the liquid is approximately 86 to 88° C. By the addition of water to the residue the strength of the solution is adjusted so that 120 c.c. contains extract from 120 grm. of Marmite.

An extract prepared by a somewhat similar method is used in nutritional anaemias of infants by Professor Leonard Parsons, to whom I am indebted for the suggestion.

The reticulocytes, red blood-cells, and haemoglobin were observed during a control period, and treatment was not commenced unless the reticulocyte percentage remained stationary, or until any slight spontaneous fluctuation had subsided. The cresyl-blue method of staining reticulocytes was used, and the preparations were counted while fresh, and without counterstain, after standing for not less than twenty minutes. Not less than 500 red blood-cells were enumerated, and the reticulocyte percentage, especially in the region of its maximum, was checked frequently by duplicate counts. Red and white blood-cells were counted under standard conditions as far as possible, using ordinary pipettes and a Bürker counting chamber. Haemoglobin percentages were estimated by the acid haematin method with a Sahli-Leitz haemoglobinometer (100 per cent. = 13·4 grm. Hbg. per 100 c.c. blood) under standard conditions. With very few exceptions, all the haematological observations were carried out personally.

It is acknowledged that under suitable conditions the character and height of the reticulocyte response forms the best indication of the potency of the substance administered. The estimation of red blood-cells and haemoglobin during a short period is much less reliable. Moreover, a material of low potency, or administered in small amounts, will frequently produce a definite but sub-maximal reticulocyte response, without any significant change in the red blood-cell count or haemoglobin percentage during a period of from ten to fifteen days (Minot, Murphy, and Stetson (21)).

In the case of the hypochromic anaemias, the reticulocytes were followed in most cases, but changes in haemoglobin percentage formed the chief measure of the potency of the preparation tested.

In order to assess the extrinsic or food deficiency factor in the aetiology of the anaemia a careful dietetic history was obtained.

The ability of the stomach to secrete free and total hydrochloric acid, chlorides, pepsin, and mucus under fasting conditions and after the administration of adequate doses of histamine (1·0 mg. for men, 0·5 mg. for women) was estimated. Unfortunately, no simple method other than

biological assay is as yet available for the estimation of intrinsic factor (Castle (4)) in the gastric juice.

Because of the scarcity of suitable cases of pernicious anaemia having a red blood-cell level under 3·0 millions per c.mm., it has been possible to carry out only a minimum number of tests with each substance to be assayed.

1. *Nutritional Hypochromic Anaemias*

A relationship between megalocytic anaemias and a factor supplied by yeast is now well established (27), but in other types of nutritional anaemia the evidence of such a relationship is less clear.

In dogs the development of hypochromic anaemia believed to be due to deficiency of some portion of the vitamin B complex, other than B_1, has been described by Suzman, Muller, and Ungley (31), who review the literature as follows: 'A number of observers have found that no anaemia occurs in rats or dogs fed diets deficient in the whole vitamin B complex. Sure, Kik, and Walker (1929), and Rose, Stucky, and Mendel (1930) using rats, and Stucky and Rose (1929) using dogs, found that there was actually an increase of haemoglobin which was attributed to anhydraemia. However, it should be pointed out that, owing to the early development of polyneuritis the dogs of Stucky and Rose received the deficient diet for periods considerably shorter (from seven to ten weeks) than those which elapsed before the onset of anaemia in our animals (from eleven to sixteen weeks) which were receiving adequate vitamin B_1. In man the consensus of opinion seems to support the view that lack of vitamin B_1 does not produce anaemia. The absence of anaemia in beri-beri was commented upon by Vedder (1913), and Keefer and Yang (1929) in a series of cases of this disease did not find anaemia in the majority of patients, although it might be quite marked when, in addition, other nutritional defects were present. With regard to the effect of deficiency of vitamin B_2, Sure, Kik, and Smith (1921) found that in rats a considerable proportion of animals developed a severe anaemia, which was especially prevalent in those with dermatitis.' Wills and Bilimoria (39) found that monkeys fed a diet composed largely of polished rice, white bread, and chapatti developed a macrocytic anaemia with a high colour index, associated with a hyperplastic bone-marrow of megaloblastic type. Vitamins A and C failed to protect the animals, but Marmite cured the anaemia. Miller and Rhoads (20) observed a syndrome resembling sprue in a proportion of dogs fed a diet partially deficient in vitamin B_2. In addition to stomatitis, glossitis, and gastro-intestinal symptoms, 30 per cent. of the animals showed a striking degree of anaemia, with a raised colour index, megalocytosis, and a megaloblastic hyperplasia of the bone-marrow quite similar to that found in cases of sprue anaemia or pernicious anaemia. In pellagra (Hillman (16)), anaemia of a variable degree exists, but it is not a prominent feature of the

disease, which may be present for a considerable time without leading to anaemia. Huck (17) observed in most cases of pellagra a slight reduction in haemoglobin and in red blood-cells, with a normal or slightly low colour index, and a normal leucocyte count, while Boggs and Padget (2) found a moderate degree of anaemia of secondary type in eighty-one out of 102 cases. On the other hand, Krjukoff (19) has reported that a blood condition resembling pernicious anaemia may accompany severe pellagra.

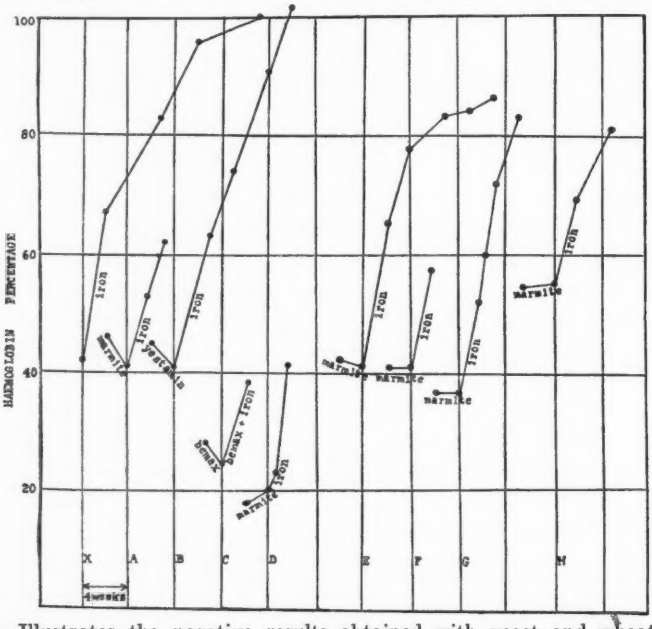

FIG. 1. Illustrates the negative results obtained with yeast and wheat embryo preparations, and the subsequent response to large doses of iron in eight cases of nutritional hypochromic anaemia, details of which are given in Table I. For clarity, many of the intermediate haemoglobin estimations have been omitted. Case 10 had iron alone from the commencement.

Guha and Mapson (15) found that rats under vitamin B_2 deficiency showed a diminution in the red cell count, which could be restored to normal by autoclaved Marmite, but not by copper, glutamic acid, extra iron, or alkaline haematin. On the other hand, the red cell count could also be restored by an autoclaved liver extract freed from vitamin B_2. Rose and Vahlteich (25), working with rats rendered anaemic by a milk diet, note that whole wheat appears to contain certain factors, lacking in patent flour, which supplement the inorganic iron and copper. The average haemoglobin increase with the ash of whole wheat was slightly less than that obtained with the original wheat.

Parsons (22 and 23) finds that the anaemia produced in rats on a milk diet can be cured not only with iron and copper, but also with yeast. This result could be achieved to a lesser extent even with yeast grown under conditions which greatly reduced its iron content (' anaemic ' yeast). Female

rats suffering from milk anaemia and treated with iron and copper usually remain unfertile even when the anaemia is cured. If yeast is used to cure the anaemia the rats become capable of reproduction, but the litters are congenitally anaemic; whereas the offspring of those cured with both yeast and iron show a haemoglobin percentage even higher than the progeny of normal stock rats fed a basal diet.

TABLE I

Case.	Sex.	Age in years.	Dietary deficiency.	Other factors.	Free HCl in gastric juice.		Initial Hb. %.	Treatment.			Reticulocyte response.	
					Resting.	Post histamine.		Dose in grm.	Duration in days.	Subsequent iron Am. citrate (grm.).	Yeast, &c.	Iron.
A	F	39	Nil	Menorrhagia	0	0	46	60–120 Marmite	10	6	4	6·4
B.	F	38	Meat	Menorrhagia	0	0	45	30 Yestamin	14	6	—	—
C	F	28	Meat, green veg.	Pregnancy, miscarriage	0	0	27	120 Bemax	10	6	Nil	—
D	F	26	—	Menorrhagia	0	++	18	60 Marmite	14	6	7·6	16·5
E	F	17	Meat, green veg.	Menorrhagia	0	0·314	44	120 Marmite	15	6	Nil	—
F	M	48	Meat?	Bleeding haemorrhoids	Trace	0·358	41	120 Marmite	12	6	Nil	5·0
G	M	9	Meat, green veg.	Nil	—	—	34	60 Marmite	13	4	5·6	6·1
H	F	2½	Meat, green veg.	Nil	—	—	54	30 Marmite	17	2–3	Nil	—

Parsons and Hawksley (23) observe that yeast is nothing like so efficacious in the treatment of nutritional anaemia of infants as it is in rats. In one case only was there complete recovery. In three cases a small reticulocyte 'kick' was obtained on the third or fourth day, and although there was a slight rise of haemoglobin of about 10 per cent., complete cure was obtained only when the yeast was supplemented by iron. In three other cases Yestamin did not produce any effect. In two cases where iron had failed to produce complete recovery that result was obtained by the addition of Yestamin. Parsons (22) suggests that the beneficial results obtained by yeast may have been due to such factors as iron (perhaps including cytochrome and haematin), copper, vitamin B, and possibly amino acids. Davidson (10) found that Marmite in doses of three to six teaspoonfuls (36 to 72 grm.) daily was ineffective in several cases of simple achlorhydric anaemia.

The results obtained with yeast and wheat germ preparations in eight cases of nutritional hypochromic anaemia are summarized in Table I and

Chart I. This number includes cases of idiopathic hypochromic anaemia with and without achlorhydria, nutritional anaemia in childhood and adolescence, and one case of delayed haemoglobin regeneration following bleeding from haemorrhoids, there having been no haemorrhage for over three months.

Very large doses of the preparations were given, as noted in Table I, but, except for a slight fluctuation of reticulocytes in three instances, no effect upon blood regeneration was noted. Subjective improvement was usually slight or absent, but cases D and E gained 7 lb. and 6 lb. respectively in two weeks. The subsequent administration of iron ammonium citrate brought about the rapid rise of haemoglobin depicted in Fig. 1, and the reticulocyte responses noted in the accompanying table.

2. *Atypical Pernicious Anaemia without Achlorhydria, Including an Unusual Case of Dysphagia with Anaemia (Pernicious)*

Yeast preparations have proved useful chiefly in those non-Addisonian megalocytic anaemias in which the deficiency of haematinic principle is probably not the direct result of lack of intrinsic factor in the gastric juice. Thus in tropical macrocytic anaemias (Wills (31)), and perhaps in certain cases of sprue, there is deficiency in foods containing the extrinsic factor, while in idiopathic steatorrhoea (35), and in some cases of sprue (6), there is probably destruction or defective absorption from the intestine of the potent material after it has been formed higher up in the gastro-intestinal tract. In these conditions gastric analysis frequently shows the presence of free hydrochloric acid, and that the intrinsic factor is also present in some cases of sprue, at least, is suggested by the work of Castle (6). The results which were obtained by Wills and Bilimoria (39) in monkeys and by Miller and Rhoads (20) in dogs provide further evidence suggesting that a macrocytic anaemia can be produced by deficiency of the extrinsic factor alone.

Although the presence of free hydrochloric acid does not necessarily mean that the stomach is secreting intrinsic factor (5), it is nevertheless desirable when testing a substance such as yeast to consider separately cases of pernicious anaemia in which there is anything less than a complete achlorhydria.

Cases of this type are not common, and Wilkinson (37) was able to collect only a relatively small number of authentic instances from the literature. The records of two such cases, each of which responded to a vegetable product rich in the vitamin B complex, are therefore reported in some detail.

The first case differed from Addisonian pernicious anaemia only in that a trace of free hydrochloric acid was present in the gastric juice after histamine stimulation, and because the diet had been grossly defective in sources of the extrinsic factor.

Case 9. M. R., a widow aged 67, entered the Massachusetts General Hospital, Boston, on August 12, 1931, suffering from pernicious anaemia, which was atypical in that free hydrochloric acid was present in the gastric juice. Her chief symptoms were abdominal pain and frequency of micturition, which were ultimately found to be due to renal calculus. The abdominal symptoms had been present for twenty-six years, but the duration of the anaemia was uncertain. She occasionally suffered from epileptiform fits, on account of which she had been forbidden to eat much meat. During the past two years she had confined herself, so far as animal food was concerned, to chicken once and bacon several times a week.

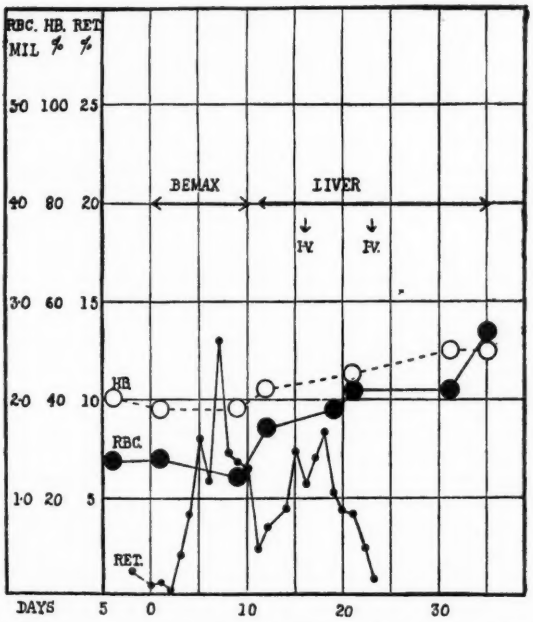

FIG. 2 (Case 9). Pernicious anaemia with hypochlorhydria and history of defective diet, showing: (*a*) Increase of reticulocytes to 13 per cent. on the 8th day during the administration of wheat embryo, averaging 5·3 oz. (160 grm.) daily. Initial red cell count 1·4 millions per c.mm., with 38 per cent. haemoglobin. Slight rise of red blood-cells to 1·7 millions per c.mm., and of haemoglobin to 42 per cent. in 11 days. (*b*) Subsequent increase of reticulocytes during the administration of 5·3 oz. (160 grm.) of prepared liver, and later of liver extract intravenously.

She was poorly nourished and pale with a yellow tint. There were ecchymoses on the tongue and purple patches on the skin of the dorsum of the hands and forearms, which she stated had been present for several months. The larger arteries were thickened and tortuous, and the heart enlarged with a systolic murmur at the apex. Moderate oedema of the legs was present. There were no evidences of neurological involvement. The urine contained pus cells and blood, and there was a mass in the right side of the abdomen which later proved to be a kidney containing a large calculus.

Gastric analysis showed twelve units of free hydrochloric acid one hour after the subcutaneous injection of histamine and an alcohol test meal.

The fasting juice and the half-hour specimen contained no free hydrochloric acid.

At the commencement of treatment there were 0·6 per cent. reticulocytes, and red blood-cells numbered 1·4 millions per c.mm., with 38 per cent. haemoglobin (Sahli-Leitz), giving a colour index of 1·36. White blood-cells numbered 4,800 per c.mm., with polymorphs 77 per cent., lymphocytes 14 per cent., monocytes 4 per cent., eosinophils 1 per cent., and myelocytes 4 per cent. The red blood-cells, which were well filled with haemoglobin, showed marked anisocytosis and poikilocytosis, many megalocytes and microcytes, slight polychromatophilia, and occasionally stippled cells. The platelets appeared to be diminished. The bleeding time and clotting time were within normal limits, and there was good clot retraction.

Detoxicated wheat embryo (Bemax) was administered for a period of ten days, in daily amounts which averaged 5·3 oz. (160 grm.), of which some was lost by vomiting. The rise of reticulocytes, red blood-cells, and haemoglobin is shown in Fig. 2. There was some subjective improvement, consisting of increased appetite and strength. (In this instance the patient was not on a completely meat-free diet, but although she was offered 2 to 3 ounces of chicken daily, she consumed only negligible quantities. It is unlikely that the amount of meat ingested was appreciably greater than that she had taken at home, and could scarcely account for the haematopoietic responses noted. In subsequent cases a completely meat-free diet was given.)

Liver was now given in doses approximately equal in weight to the average daily consumption of Bemax, namely 5·3 oz. (160 grm.) daily. On the fifth day of liver therapy, it was decided to expedite recovery in order that an operation on the kidney might be performed. For this reason extract No. 343 (N. N. R.) derived from 100 grm. of liver was given intravenously (7) on the fifth and twelfth days. However, it is clear from the secondary rise of reticulocytes which had already occurred by the fifth day of liver therapy *per os*, that the liver was considerably more potent than the wheat embryo preparation. The right kidney removed at operation was found to be the seat of acute and chronic pyelonephritis, and to contain a single large stone.

The second case had the clinical features of the Plummer-Vinson syndrome (dysphagia with anaemia), except that the blood picture was macrocytic in type. Free hydrochloric acid was secreted after histamine stimulation, and the diet had been markedly defective in fresh meat and green vegetables.

Case 10. J. H., a married woman, 39 years of age, admitted to the Royal Victoria Infirmary, Newcastle-upon-Tyne, under Dr. Drummond on August 20, 1932, complained that for seven years she had had difficulty in swallowing, the food sticking at the pharyngo-oesophageal junction. The dysphagia was more for solid foods than for liquids, and occurred in attacks lasting two or three weeks, with intervals of two to three months' freedom. She had always been pale, but during the past sixteen years the pallor had been more marked, with periodic exacerbations; the ankles were frequently oedematous. Menstruation began at the age of 18, after treatment with Blaud's pills. For the past six or seven years the menses had been scanty, occurring at intervals of three to five months. The tongue had been sore intermittently for two years. Eight months ago she suffered for three weeks from pain and vomiting one hour after food; apart from this there was no history of gastro-intestinal disturbances. During the past eight

months she had lost weight, the anaemia had increased, and there had been dyspnoea and palpitation on exertion. The appetite remained good until one month ago, and the bowels were always regular. The teeth were removed six months ago for pyorrhoea. There were no paraesthesiae or other neurological symptoms, apart from headaches, which had troubled her for sixteen years. She attributed all her symptoms to venereal disease, which she thought she had contracted from her husband sixteen years previously. She stated that a heavy vaginal discharge had been present intermittently since that time. Repeated examinations and many negative Wassermann tests had failed to convince her that she had neither syphilis nor gonorrhoea.

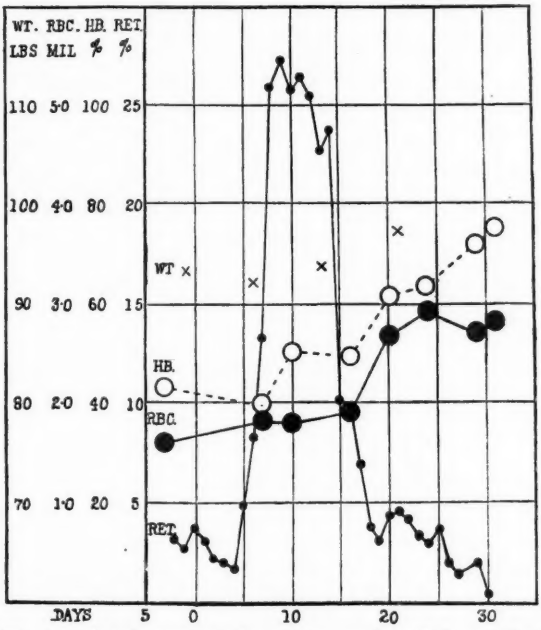

FIG. 3 (Case 10). Dysphagia and megalocytic anaemia with hypochlorhydria, showing somewhat prolonged reticulocytosis with a peak of 27·2 per cent. on the 9th day, during the administration of Marmite 4 oz. (120 grm.) daily. Initial red cell count of 1·6 millions per c.mm. with 43 per cent. haemoglobin. Rise of red blood-cells to 2·83 millions and of haemoglobin to 75 per cent. in 31 days.

The diet for many years had consisted largely of bread, butter, jam, and tea. She ate meat about three times a week unless suffering from dysphagia. The chief vegetable constituents of the diet were potatoes and dried peas, with cabbage only once in two weeks. The consumption of fresh milk was less than one pint per week.

The past history was negative except for acute nephritis at the age of 14. Her mother died at the age of 71, having been bedridden for four years with 'neuritis', and having been anaemic all her life. Two sisters and three brothers are alive and well, but all are said to be pale. The father died at 60 with heart trouble. She has one child, a mentally deficient boy of 17.

Six months before admission she commenced to take cooked liver, $\frac{1}{4}$ lb. three or four times a week, but had taken none during the past two months, owing to dysphagia and indigestion.

Examination showed a rather under-nourished, pale, nervous woman, with scanty brown hair and a somewhat dry skin. There was no noticeable icterus. The tongue was completely smooth and shiny, and the teeth artificial. Physical examination was otherwise normal. The finger nails were normal, and there was no enlargement of the spleen or liver.

X-ray examination after a barium bolus showed no obstruction, stenosis, or residue, but at oesophagoscopy there was marked spasm of the pharyngo-oesophageal junction, which failed to yield access to any bougie, even after the prolonged application of a 10 per cent. cocaine mop. The mucosa was pallid, but otherwise normal.

The first attempt at passing a nasal test-meal tube failed, partly because of actual dysphagia, but also because the patient was highly nervous. A second attempt three weeks later, after she had been in hospital a few days, was successful, although great difficulty was experienced in getting the tube into the upper oesophagus. No free acid was present in the fasting juice, but half an hour after the subcutaneous injection of 0·5 mg. histamine, a small amount of free hydrochloric acid was secreted (0·033 per cent.). Pepsin, tested for in the one-hour specimen, which contained no free HCl, was present to the extent of 4 units (Fuld's method).

Contrary to expectations, the blood picture was that of pernicious anaemia. The findings on admission were as follows: red blood-cells 1·6 millions per c.mm., haemoglobin 43 per cent. Sahli-Leitz, colour index 1·3, reticulocytes 3·2 per cent., white cells 8,250 per c.mm. A differential count showed: neutrophils 47 per cent., lymphocytes 44 per cent., monocytes 8 per cent., eosinophils 1 per cent.

The red blood-cells showed marked anisocytosis with slight poikilocytosis, and numerous oval megalocytes. Measurements showedthat the average diameter of the red blood-cells was 8·95μ, with 1·7μ dispersion.[2] With a fragility-test unwashed red corpuscles underwent initial haemolysis in 0·50 per cent. NaCl solution, and 90 per cent. haemolysis in 0·30 per cent. NaCl solution.

The administration of Marmite in doses of 4 oz. (120 grm.) daily was followed by the haematopoietic response illustrated in Fig. 3. In this case Marmite caused colic and diarrhoea, for which a chalk and opium mixture was at times necessary.

After leaving hospital the consumption of Marmite was rather less, averaging 3 to $3\frac{1}{2}$ oz. daily. From the following figures it will be seen that the rate of blood regeneration was somewhat slow:

6th week	R.B.C. 2·52	Hb. 69	9th week	R.B.C. 3·16	Hb. 78
7th week	R.B.C. 2·97	Hb. 80	12th week	R.B.C. 4·43	Hb. 81

There has been no dysphagia and no soreness of the tongue since the commencement of treatment.

3. *Addisonian Pernicious Anaemia*

The haematopoietic effect of yeast preparations in certain non-Addisonian megalocytic anaemias has already been discussed. In classical pernicious anaemia negative results were reported in 1928 by Cohn, Minot, Alles, and Salter (8) who used yeast cake in doses of 120 grm. daily and various concentrates of vitamin B. The reticulocyte response observed in 1930 in a

[2] As measured with an ocular micrometer, using the method of Bell, Thomas, and Means (*Journ. Clin. Investig.*, 1926, iii, 229). By this method the normal median is 7·8 to 7·9μ, with a dispersion of 1·0μ.

case of pernicious anaemia during the administration of Bemax in doses of 270 grm. daily formed the starting-point of this present work, and has already been mentioned. In 1931 Gilroy (13) recorded observations on the vitamin B content of commercial liver extracts and stomach preparations, and discussed the relationship between vitamin B and anaemia. In the same year Davidson (10) described a mildly positive effect in one case, and a negative response in two others, from Marmite, 3–6 teaspoonfuls [3] (36–72 grm. daily). Carmalt-Jones (3) noted the diuretic effect of Marmite and of tiki-tiki in two cases of pernicious anaemia. Goodall (14) reported positive results in three cases of pernicious anaemia in relapse from the administration of Marmite alone in doses of 1 tablespoonful [3] three times a day (about 150 grm. daily), and discussed the use of smaller doses in maintenance cases. Since this paper was submitted for publication Professor L. S. P. Davidson has kindly sent me details of a total of thirteen cases treated with Marmite in doses of from 36 to 150 grm.,[3] of which nine failed to respond, and four showed a definite but usually submaximal response.

Strauss and Castle (27) found that autolysed yeast in doses of 12 grm. daily had no effect upon blood formation, but that maximal responses followed the administration of 12 grm. of autolysed yeast activated with normal gastric juice. Similar results were recorded when the yeast was autoclaved to destroy vitamin B_1 before activation, and also when the majority of protein and nucleoprotein was excluded by extraction with 80 per cent. alcohol. Yeast nucleic acid incubated with normal gastric juice gave negative results. The authors conclude that the extrinsic factor is probably either vitamin B_2 or some substance closely allied to it.

Fouts, Kempf, Greene, and Zerfas (11) administered intravenously an extract of vitamin B (containing chiefly B_1, little B_2), over periods of from one to more than seven months, to six cases of pernicious anaemia having central nervous system involvement. There was no improvement in the neurological findings, and the extract, when given intravenously, was not able to maintain the red blood-cells of the patients at their original level.

The results obtained from the administration of massive doses of wheat germ and yeast preparations will now be described.

A. *Wheat germ.* Wheat germ, which is a potent source of vitamin B_1, and also contains vitamin B_2, was administered in the form of Bemax in doses of 160–270 grm. daily to three patients with classical pernicious anaemia.

Case 11. A male, aged 47, had Addisonian pernicious anaemia and subacute combined degeneration of fifteen months' duration. It was decided to observe the effect, if any, of vitamin B on the neurological condition in view

[3] The dosage of Marmite in the reports of Wills, Vaughan and Hunter, Davidson, Goodall, and others has been expressed in tea- and tablespoonfuls. According to Davidson (personal communication) a level teaspoonful of Marmite weighs about 12 grm., a heaped teaspoonful 30 grm., and a tablespoonful 50 grm.

of the work of Cowgill (9) and of Gildea, Kattwinkel, and Castle (12). Vitamin B was given in the form of desiccated embryo of wheat (Bemax) in doses of 270 grm. daily for thirty-two days. During this period there occurred an increase of reticulocytes to 11·8 per cent. on the eleventh day. From an initial level of red blood-cells of 1·02 millions per c.mm., with 36 per cent. haemoglobin, the count rose in twenty days to 1·4 millions with 48 per cent. haemoglobin. The haemoglobin percentage subsequently fell following diarrhoea of several days' duration.

There was some increased sense of well-being, though less than that which occurs with liver therapy. Paraesthesiae were unaffected, and there was no significant change in the neurological condition.

In this case, which has been described fully elsewhere (32), the Bemax was not being tested specifically for haematopoietic effect, and since the reticulocytes were rising when the vitamin B preparation was first given the possibility of a spontaneous remission cannot be excluded. Although at this time (1930) the importance of a completely meat-free diet was not realized, the ordinary hospital diet which he received did not contain amounts of meat significantly greater than he had taken at home.

In two other cases of classical pernicious anaemia, the administration of Bemax was without effect upon blood regeneration.

Case 12. H. N., a married woman, 60 years of age, entered the Massachusetts General Hospital, Boston, on August 24, 1931, suffering from pernicious anaemia and subacute combined degeneration of the cord. Symptoms referable to anaemia began two years previously, and responded to liver therapy, so that she felt normal in three months. Nine months later the symptoms recurred, together with numbness of the fingers and soreness of the tongue; liver treatment again gave relief. Three months before entry she relapsed once more, and soon afterwards noticed numbness in the lower extremities and difficulty in walking. One brother had died from probable pernicious anaemia at the age of 66 years.

On examination there was pallor with a slight yellow tint, and a palpable spleen. The ankle jerks were absent, and joint sense was diminished in the feet. A chronic purulent dacryocystitis was present. Gastric analysis after an alcoholic test meal and the subcutaneous injection of histamine showed complete achlorhydria, with a low total acidity.

At the commencement of treatment red blood-cells numbered 1·9 millions per c.mm., with 50 per cent. haemoglobin (Sahli-Leitz), the colour index being 1·3. White blood-cells numbered 6,200 per c.mm., with polymorphs 43 per cent., lymphocytes 48 per cent., monocytes 5 per cent., and eosinophils 4 per cent. The red blood-cells, which were well filled with haemoglobin, showed considerable anisocytosis and poikilocytosis, with many megalocytes.

Bemax was given for ten days in daily amounts, which averaged 4·1 oz. (123 grm.), some of this being lost by vomiting. There was an insignificant rise of reticulocytes to 4·3 per cent. on the sixth day, and a little subjective improvement, but no increase of red blood-cells or haemoglobin. The administration of equal amounts of liver by mouth was abandoned owing to anxiety as to her clinical condition. The subsequent daily intramuscular injection of liver extract derived from 10 grm. of liver resulted in a reticulocyte response, which reached 21·3 per cent. on the sixth day, and a rapid rise of red blood-cells and haemoglobin.

Case 13. J. C., male, a clerk aged 55, was admitted to the Massachusetts General Hospital, Boston, suffering from pernicious anaemia of nine years' duration. Liver therapy was commenced three years after the onset, and he had remained well until six weeks before entry, when he again complained of weakness, dyspnoea, and numbness of the fingers and toes. He stated that he had eaten small amounts of liver two or three times a week for the past month. Examination showed a well-developed and fairly well nourished man, markedly pale with a yellow tint. The icterus index was 23.

At the commencement of treatment red blood-cells numbered 870,000 per c.mm., with 18 per cent. haemoglobin (Sahli-Leitz), the colour index being 1·03. White blood-cells numbered 4,000 per c.mm. The appearances of the blood film were typical of pernicious anaemia.

Bemax was given in doses of 8 oz. (240 grm.) daily for ten days. There was a negligible rise of reticulocytes to 2·6 per cent. on the sixth day, and no significant increase in red cells or haemoglobin. The subsequent daily injection of liver extract derived from 10 grm. of liver, together with 240 grm. of raw liver by mouth, resulted in a reticulocyte response of 18·3 per cent. on the fourth day, and an increase of red blood-cells to 1·85 millions per c.mm. in seven days.

The haematopoietic effect from wheat germ observed in a case of pernicious anaemia, atypical in that a trace of free hydrochloric acid was present in the gastric juice, has already been described in Section 2 of this paper. Negative results followed the use of Bemax in nutritional hypochromic anaemia, as reported in Section 1.

B. *Yeast preparations.* Marmite in doses of 60 to 120 grm. was administered to five cases of Addisonian pernicious anaemia, and two further cases received an alcoholic extract of Marmite. Dried yeast (Yestamin) was used in one instance, but it was found impossible to get the patient to take more than an average of 48 grm. daily.

In one other case, not included in this series, the administration of Marmite was discontinued on the sixth day owing to abdominal pain, which proved to be due to paratyphoid fever. Although a rise of reticulocytes, red blood-cells, and haemoglobin ensued, no deductions could be drawn because of the presence of infection and possible dehydration.

Case 14. Positive result from Marmite, 60 grm. daily. T. C., a miner, 45 years of age, entered the Royal Victoria Infirmary, Newcastle-upon-Tyne, on April 6, 1932, suffering from pernicious anaemia of three years' duration. Eighteen months previously, when his initial red blood-cell level was 2·23 millions per c.mm., he had responded to desiccated stomach therapy, showing a reticulocyte response of 18·5 per cent. on the eleventh day, and an increase of one million red cells in that time. After leaving hospital he took cooked liver in small quantities irregularly. Five months ago he began to suffer from weakness, dyspnoea, and anorexia, and more recently he complained of soreness of the tongue and numbness and tingling in the finger tips. The tongue was clean, with atrophy of the papillae at the edges. The spleen was just palpable. Neurological examination showed defect in co-ordination and in joint sense, chiefly in the lower limbs; the ankle jerks were absent, and the plantar reflexes flexor.

Gastric analysis showed complete achlorhydria, even after the injection of 1 mg. histamine, and only a trace of pepsin was present in any specimen (less than two units by Fuld's method); neutral red given intramuscularly was not excreted into the gastric juice during a period of one and a half hours.

At the commencement of treatment the red blood-cell count was 1·42 millions per c.mm., with haemoglobin 38 per cent. (Sahli-Leitz), giving a colour index of 1·3. White blood-cells numbered 4,800 per c.mm.

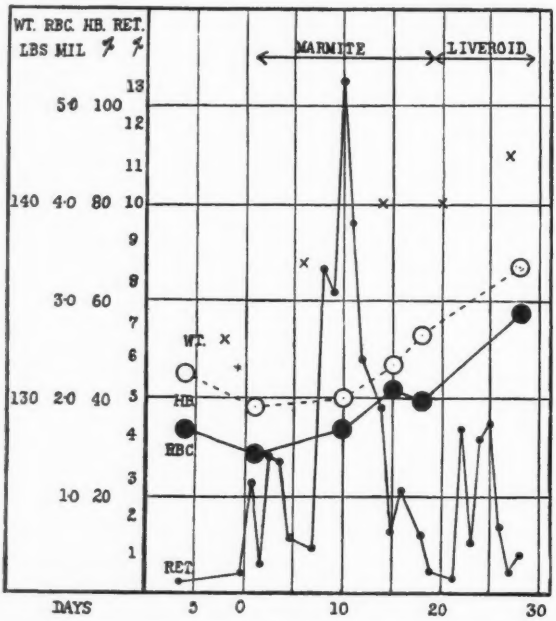

FIG. 4 (Case 14). Pernicious anaemia, showing: (*a*) Increase of reticulocytes to 13·1 per cent. during the administration of Marmite, 2 oz. (60 grm.) daily. Initial red cell count 1·42 millions per c.mm., with 38 per cent. haemoglobin. Rise of red cells to 2·0 millions per c.mm. and of haemoglobin to 53 per cent. in 18 days. (*b*) Second rise of reticulocytes to 4·4 per cent. on the 7th day from Liveroid, 2 oz. daily (equals amount derived from 240 grm. of liver). Rise of red cells to 2·9 millions and of haemoglobin to 67 per cent. in 10 days.

The haematopoietic response to Marmite in doses of 2 oz. (60 grm.) daily is illustrated in Fig. 4. Soreness of the mouth and tongue, and dryness of the mouth disappeared after about a week, and the appetite greatly improved. At the end of two weeks he noticed increased strength, less dyspnoea, and returning colour in his hands. The paraesthesiae remained unchanged. His weight increased by 7 lb. 3 oz., as shown on the chart. Marmite was then discontinued and an equal quantity of liver extract (i.e. Liveroid 2 oz., which is the amount derived from 240 grm. of liver) was given daily. The secondary rise of reticulocytes indicated that the liver extract was the more potent preparation.

Case 15. Positive result from Marmite, 120 grm. daily. H. C., a miner, 58 years of age, was admitted to the Royal Victoria Infirmary on June 8, 1932, suffering from pernicious anaemia of eight months' duration. Numbness in the fingers and in the soles of the feet, and symptoms referable to

anaemia had been present for eight months. For six months there had been severe diarrhoea, and soreness of the tongue. He was pale with a yellow tint. The tongue was clean, with atrophy of papillae at the edges, and marked pyorrhoea was present. The radial arteries were thickened. No enlargement of the liver or spleen was detected. He had not had liver therapy at any time.

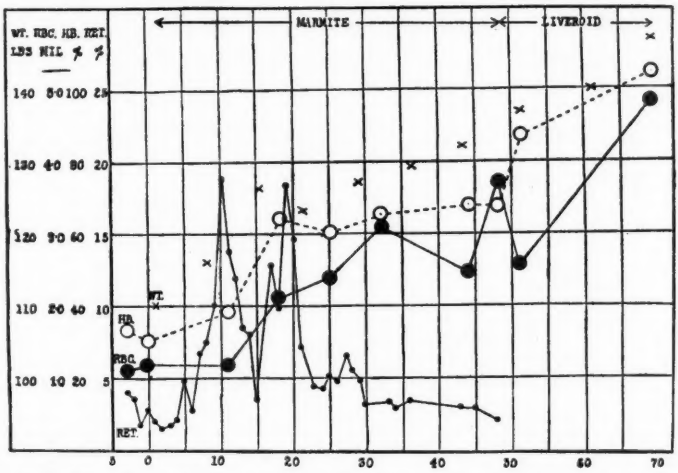

FIG. 5 (Case 15). Pernicious anaemia, showing: (*a*) Increase of reticulocytes to 18·6 per cent. on the 10th day, followed by a second rise to 18·2 on the 18th day, during the administration of a fixed dose of Marmite 4 oz. (120 grm.) daily. Initial red cell count of 1·16 millions per c.mm., with 30 per cent. haemoglobin, and 1·8 per cent. reticulocytes. Rise of red blood-cells to 3·8 millions per c.mm., with 68 per cent. haemoglobin, and a gain of 27 lb. in weight in 7 weeks. (*b*) Further increase in red cells, haemoglobin, and body weight during the administration of Liveroid 4 oz. daily (equals liver extract derived from 480 grm. of liver).

Gastric analysis showed complete achlorhydria, even after the subcutaneous injection of 1 mgm. of histamine. A trace of pepsin was present, only two units by Fuld's method. Neutral red had not been excreted into the gastric juice an hour after its injection. At the commencement of treatment red blood-cells numbered 1·16 millions per c.mm., with haemoglobin 30 per cent., giving a colour index of 1·5. White blood-cells numbered 3,550 per c.mm. Stained films were characteristic of pernicious anaemia.

The haematopoietic effect of Marmite in doses of 4 oz. daily is shown in Fig. 5. An unusual feature of the reticulocyte response in this case is that, although the dose of Marmite remained unchanged, there were two reticulocyte peaks, the first on the tenth and the second on the nineteenth day. The possible significance of this finding is discussed later. The white cell count rose to normal. Soreness of the tongue ceased after the ninth day and numbness of the hands after two weeks. The appetite returned, and as seen in the chart, the weight increased rapidly, so that he gained 22 lb. in six weeks. The evening temperature stayed at about 99 F. until the eleventh day when it fell to normal and remained so.

The increase of red blood-cells and haemoglobin percentage continued at about the same rate during the subsequent administration of liver extract (Liveroid) in equal dosage, i.e. 4 oz. daily, this being the amount derived from 480 grm. of liver.

Case 16. Positive result from Marmite, 120 grm. daily. A. N., male, aged 47, admitted to the Royal Victoria Infirmary, Newcastle-upon-Tyne, on August 4, 1932, under Dr. Nattrass, suffered from pernicious anaemia of one year's duration. The tongue had been sore for two months. He showed pallor with a yellowish tint, a clean tongue with atrophy of papillae, and a spleen which was palpable one finger's breadth below the costal margin. There were no neurological symptoms or signs.

Gastric analysis revealed complete achlorhydria, even after 1 mg. of histamine subcutaneously.

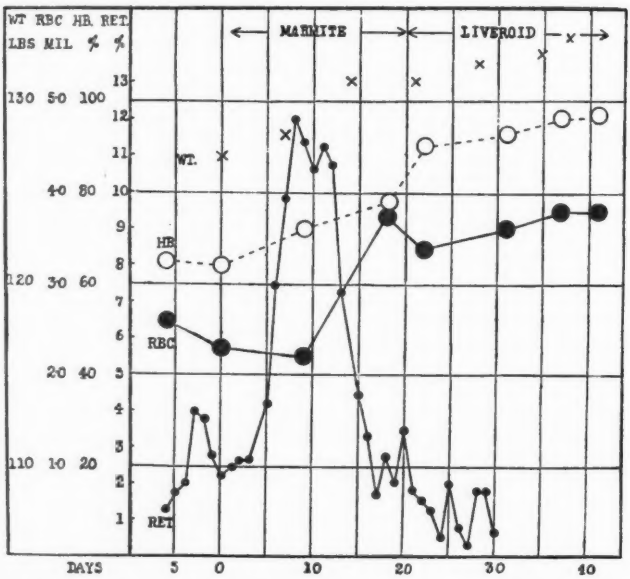

FIG. 6. (Case 16). Pernicious anaemia, showing: (*a*) Increase of reticulocytes to 12·0 per cent. during the administration of Marmite 4 oz. (120 grm.) daily. Initial red cell count 2·3 millions per c.mm., with haemoglobin 64 per cent. Rise of red blood-cells to 3·4 millions per c.mm., with haemoglobin 90 per cent. in 3 weeks, and an increase of 4 lb. in weight. (*b*) Subsequent increase in red blood-cells, haemoglobin, and body weight during the administration of Liveroid 4 oz. daily (equal to the amount derived from 480 grm. of liver).

At the commencement of treatment red blood-cells numbered 2·3 millions per c.mm., with 64 per cent. haemoglobin, giving a colour index of 1·3. Fig. 6 illustrates the reticulocyte response and the rise of red cells and haemoglobin which followed the administration of Marmite in doses of 4 oz. (120 grm.) daily. There was marked subjective improvement at the end of the first week, and an increase in weight of four pounds in twenty days. As the tongue was not sore at any time during his hospital stay it was not possible in this case to judge the effect of Marmite on this symptom.

The effect of the subsequent administration of liver extract (Liveroid) in daily doses of 4 oz., i.e. the amount derived from 480 grm. of liver, is illustrated on the chart; the fact that there was no secondary reticulocyte rise, may have been due to the high red blood-cell level at the time liver extract was commenced.

Case 17. Slow response to Marmite 60–120 grm. daily, and later to Marmite and iron. R. F., a married woman, aged 68, was admitted to the Royal Victoria Infirmary under Dr. Drummond on October 24, 1932, suffering from pernicious anaemia of two years' duration. Soreness of the tongue and of the gums was present, and swallowing was painful. The tongue was red at the tip and showed marked atrophy of papillae at the sides. There were no neurological symptoms, and the spleen was not palpable. No free hydrochloric acid was secreted after a test meal of gruel, and a subsequent test showed complete achlorhydria even after the subcutaneous injection of 0·5 mg. of histamine.

The patient left hospital after a short stay, but subsequently attended regularly for blood examination. At the commencement of treatment the red blood-cells numbered 2·69 millions per c.mm., with 70 per cent. haemoglobin, giving a colour index of 1·3. White blood-cells numbered 5,300 per c.mm., and reticulocytes 2·0 per cent.

For ten days the consumption of Marmite was about 4 oz. (120 grm.) daily. At the end of this period the red blood-cells numbered 2·89 millions per c.mm., with 80 per cent. haemoglobin. The tongue was less sore, swallowing was easier, and the patient felt stronger.

From the tenth day onwards there was some difficulty in taking full quantities of Marmite, and the consumption averaged only 2 oz. (60 grm.) daily. Diarrhoea occurred for three days during the third week, but the bowels were subsequently normal or slightly constipated. The tongue ceased to be sore after three weeks, and discomfort on swallowing ceased a week later. Numbness and tingling in the hands occurred for the first time during the third week of treatment and involved the feet two weeks later. During the ninth week the paraesthesiae increased in intensity. The appetite increased, but there was no significant alteration of body weight.

The blood improved slowly, and on the twenty-fifth day the red blood-cell count was 3·27 millions per c.mm., with 84 per cent. haemoglobin. From this point the blood condition remained stationary, so that at the end of nine weeks the red blood-cells numbered 3·41 millions per c.mm., with 84 per cent. haemoglobin.

In certain cases of pernicious anaemia treated with liver extract it is difficult to bring the blood condition beyond a certain level without the addition of iron (Beebe and Lewis (1)). Because it was thought that a similar measure might be useful in this instance, the patient was now given iron ammonium citrate 6 grm. daily in addition to the Marmite, the daily consumption of which thereafter averaged only 40 grm. In spite of an intercurrent attack of influenza, gradual improvement followed, and the red blood-cells reached 4·53 millions, with 96 per cent. haemoglobin at the end of four weeks. On the other hand, numbness and tingling in the extremities were gradually increasing in extent and in intensity, and for this reason Marmite and iron were discontinued in favour of a liver diet.

After taking daily for four weeks cooked liver in doses of 120 grm. (as bought), there was no further change in the red blood-cell count or haemoglobin percentage, but the paraesthesiae diminished in extent and severity.

Case 18. Negative result from Marmite and Yestamin, followed by a poor response to liver. M. B., a married woman, aged 48, admitted to the Royal Victoria Infirmary on July 1, 1932, suffered from pernicious anaemia of sixteen weeks' duration. The tongue was clean and absolutely smooth. Both liver and spleen were palpable below the costal margin. There were

no neurological symptoms. She had been taking small doses of liver extract daily for two months. Gastric analysis showed complete achlorhydria, even after ½ mg. of histamine subcutaneously. Only four units of pepsin (Fuld) were present in the gastric juice obtained after histamine stimulation.

At the commencement of treatment the red blood-cells numbered 1·37 millions per c.mm., with 30 per cent. haemoglobin (Sahli-Leitz), giving a colour index of 1·1; the white cells numbered 5,050 per c.mm.

An attempt was made to administer dried yeast (Yestamin) in doses of 4 oz. daily. In a period of ten days she was able to consume only 16 oz., of which some was lost by vomiting. From an initial 1 per cent., the reticulocytes rose only to 5 per cent. on the fourth day, and there was no increase of red cells or haemoglobin. The subsequent administration of Marmite in doses of 4 oz. (120 grm.) daily for nine days was without haematopoietic effect. Cooked liver, ½ lb. (240 grm.), daily was then given, but at the end of two weeks the red blood-cells had risen only 0·5 million, and the haemoglobin 16 per cent., indicating that larger doses were necessary, and that the case was relatively resistant to liver treatment administered orally.

Two further cases of Addisonian pernicious anaemia received a 65 per cent. alcoholic extract of Marmite. A full report of these cases forms part of a subsequent paper (33) which concerns attempts made to determine the nature of the active principle in yeast, but the results may be summarized here.

TABLE II

Case.	Age.	Treatment.	Duration.	Hb.	R.B.C.	Reticulocytes.
19	52	Alcoholic extract of	1 day	46	1·65	(3·6) 8·8 % on
Mrs. H. D.		Marmite from	10 days	54	2·05	9th day
		120 grm. for 42 days	24 ,,	64	2·45	
			42 ,,	90	3·58	
20	58	Alcoholic extract	1 day	40	1·34	(3·7) 27·2 % on
Mr. H. S.		from Marmite	12 days	56	2·26	10th day
		120 grm. for 58 days	22 ,,	66	2·93	
			30 ,,	80	3·39	
			44 ,,	90	4·07	
			51 ,,	98	4·89	
			58 ,,	97	5·12	

The fairly high initial reticulocyte percentage in each case is due to previous therapy of low potency, the slight fluctuation of the reticulocyte count not having completely subsided when the alcoholic extract was commenced. The haematopoietic effect in these two cases was accompanied by marked subjective improvement, and an increase in appetite and weight.

Discussion

1. *Nutritional hypochromic anaemias.* Much of the animal experimental work reviewed above suggests a relationship between hypochromic anaemias and a factor supplied by yeast and wheat germ, and which is perhaps some portion of the vitamin B complex other than vitamin B_1. Apart from the occasional results with yeast in hypochromic anaemias in infants as reported by Parsons and Hawksley (23), there is at present little evidence of such

a relationship in man. From the present work it will be seen that in nutritional hypochromic anaemias, with or without achlorhydria, and whether or not the diet had been grossly defective, no effect upon haemoglobin regeneration followed the administration of massive doses of yeast or wheat germ preparations. The slight reticulocytosis noted in three out of eight cases is of interest in view of the observations of Parsons and Hawksley (23) that some infants treated with Yestamin showed a small reticulocyte 'kick' without much increase in haemoglobin percentage. It is also interesting to note in passing that the presence or absence of achlorhydria or of a defective diet did not appear to influence the rate of the subsequent haemoglobin regeneration with iron. The possible value of yeast and wheat germ in supplementing small doses of iron is being investigated. The animal experiments of Parsons (22) suggest that yeast as well as iron may be indicated in the hypochromic anaemia of pregnancy.

2. *Atypical pernicious anaemia without achlorhydria.* Both Marmite and Bemax had some haematopoietic effect in the two patients in this group, who showed an incomplete defect in the gastric secretion of free hydrochloric acid, combined with a gross dietary deficiency. Autolysed yeast, and probably wheat germ, are potent sources of the extrinsic factor, and the results may have been due to the fact that intrinsic factor was not completely absent from the gastric juice. On the other hand, the responses were submaximal in degree like those usually obtained from Marmite in classical pernicious anaemia, in which intrinsic factor is presumed to be absent, and in contrast with the marked responses obtained in certain megalocytic anaemias believed to be due to causes other than defective gastric secretion of the intrinsic factor, namely, tropical macrocytic anaemias, and complicating idiopathic steatorrhoea. The small magnitude of the response in the first case may have been due to septic complications, however, and it is noteworthy in this connexion that the subsequent response to liver, both orally and parenterally, was also slow.

3. *Addisonian pernicious anaemia.* Of the ten cases of classical pernicious anaemia treated with yeast and wheat germ preparations, seven showed a response of greater or less degree, and three failed to respond.

Wheat germ in the form of Bemax gave an uncertain positive result in one case and negative results in two others. The submaximal response obtained in one case of atypical pernicious anaemia was noted in section 2. The results obtained with wheat germ were on the whole discouraging, and considerable difficulties were encountered from digestive disturbances because of the large amounts used. In later experiments yeast preparations only have been employed. Yeast preparations gave positive results of greater or less degree in six out of seven cases of classical pernicious anaemia, and also in one case of atypical pernicious anaemia as noted in section 2. Marmite itself in doses of 60 to 120 grm. was used in all except two cases, which received a 65 per cent. alcoholic extract of this preparation. Dried yeast (Yestamin) was used in one instance, but it was found impossible to

get the patient to take more than an average of 48 grm. daily. The administration of large doses of yeast preparations is not always easy owing to digestive disturbances, but the discovery that a 65 per cent. alcoholic extract of Marmite is effective has overcome this difficulty.

In addition to the effect of Marmite on blood regeneration and upon symptoms referable to anaemia, there occurred an increase in the sense of well-being, and a marked increase in appetite. Soreness of the tongue when present usually disappeared within ten days of the commencement of treatment. Digestive symptoms such as flatulence and epigastric discomfort were ultimately improved, although nausea and even vomiting sometimes occurred in the early stages of administration. Marmite had a mildly laxative effect in most cases, sufficient to keep the bowels regular in those who were previously constipated. The occasional occurrence of troublesome diarrhoea made it advisable to withold purgatives during treatment.

An increase in weight associated with the improvement in appetite which occurred chiefly in the megalocytic anaemias and scarcely at all in the hypochromic anaemias, was probably analogous to that which accompanies liver therapy (34) rather than an effect specifically due to any of the vitamins of yeast.

Paraesthesiae disappeared in one case, were unaffected in another, and appeared during therapy in a third. The addition of yeast preparations to the diet of cases not described in this paper, whose neurological symptoms were stationary or progressing on inadequate doses of liver was without effect in two instances, and led to marked improvement in a third. Yeast and wheat germ preparations have not been administered alone to patients with subacute combined degeneration for lengths of time sufficient to judge their effect in this condition.

In most cases the character of the reticulocyte response was similar to that which follows the administration of other substances known to be potent for blood regeneration in pernicious anaemia, e.g. liver, kidney, stomach, brain, predigested meat. The peak of the response occurred on the eighth, ninth, or tenth day. In Case 15, on the other hand, a reticulocyte response on the tenth day was followed by another very similar response on the eighteenth day, although the dosage of Marmite and the conditions of the experiment remained constant. However, the possibility of variation of anti-anaemic potency in different batches of Marmite cannot be ruled out.

At a given initial level of red blood-cells, and in carefully selected cases, the height of the reticulocyte response is proportional to the potent amount of the material administered (21). It will be noted (Table III) that the peak of reticulocytes reached was usually less than the expected maximum rise for the initial level in question (24), as calculated from the formula:

$$R = \frac{0{\cdot}73 - 0{\cdot}2\,E_o}{0{\cdot}73 + 0{\cdot}8\,E_o},$$

where R represents the maximum reticulocyte percentage observed during treatment, and E_o the red blood-cell count before treatment. Moreover, the reticulocyte response was usually somewhat slow, with the peak on the eighth, ninth, or tenth day.[3]

TABLE III

Case.	Initial R.B.C.	Expected maximal retic. response.	Observed retic. response.	Day dose (grm.)	Calc. amt. prepared liver to give same R.R.	Subsequent response to liver.
9	1·4	24·3	13·0	160 Bemax	160+	Poor
11	1·02	34·6	11·8	270 Bemax	120	Good
12	1·9	15·6	Neg.	123 Bemax	—	Good
13	0·87	38·0	Neg.	240 Bemax	—	Fairly good
10	1·6	20·4	27·2	120 Marmite	400	—
14	1·42	24·3	13·1	60 Marmite	160–170	Good
15	1·16	29·0	18·6	120 Marmite	230	Good
16	2·3	10·5	12·0	120 Marmite	250	Fair
17	2·69	6·6	Not obs.	120 Marmite	—	—
18 i	1·37	24·3	Neg.	48 Yestamin	—	Poor
ii	1·2	29·0	Neg.	120 Marmite	—	
19	1·65	18·7	8·8	Ext. from 120 Marmite	160	Good
20	1·34	26·5	27·2	Ext. from 120 Marmite	350	—

From the curves constructed by Minot, Murphy, and Stetson (21) it is possible to calculate approximately the amount of liver which would be required to give responses similar to those obtained (Table III). The data in respect to wheat germ (Bemax) are inadequate, but suggest the possible presence of small amounts of material potent for pernicious anaemia. From the results shown in Table III, together with others since obtained with an alcoholic extract of marmite (33), it would appear that the reticulocyte response to this substance is comparable to that which would be expected from about twice the amount of whole liver (prepared weight). On the other hand, the rate of increase of mature red blood-cells was as a rule less rapid than that which follows the administration of the usual optimal amounts of potent material (21), and often less than the height of the reticulocyte response led one to expect. For this reason, and because the results are so variable, it is difficult to assess accurately the potency of Marmite relative to that of liver.

[3] i.e. 7th, 8th, or 9th day *after* the commencement of treatment, counting the first day of treatment as 0.

From the therapeutic point of view, however, the variable and usually submaximal results obtained with doses, as large as can be tolerated, indicate that none of the preparations used is a satisfactory substitute for liver in the relapse stage, while in the stage of haematopoietic remission adequate doses of potent material, especially in the form of whole liver, are desirable for the prevention and treatment of subacute combined degeneration. Marmite is sometimes of value as a supplement to other therapy, however, and may be used with advantage in place of orange juice as a flavouring medium for the administration of raw liver pulp. The results so far obtained with a 65 per cent. alcoholic extract of Marmite suggest the possibility that an inexpensive product suitable for the treatment of pernicious anaemia may yet be obtained from yeast.

The results are chiefly of interest in connexion with the aetiology of pernicious anaemia, especially with regard to the factors necessary for haematopoiesis. Yeast preparations may owe their potency to one or more of the following factors: (1) extrinsic factor; (2) a breakdown product of the extrinsic factor, perhaps resulting from the interaction of this substance with an enzyme liberated during the autolysis of yeast; (3) small quantities of a substance resembling the 'liver active principle'. These three possibilities will now be considered in more detail.

1. Cases of pernicious anaemia may perhaps respond to yeast and wheat germ preparations only if there is some intrinsic factor in the gastric juice. Marmite is obviously much less potent for classical pernicious anaemia than for certain megalocytic anaemias without achlorhydria which are believed to be due to causes other than defective secretion of the intrinsic factor, namely tropical macrocytic anaemia and complicating idiopathic steatorrhoea. The massive doses required, the smaller responses obtained, and the variability of the results might be due to the presence in many cases of Addisonian pernicious anaemia of small and varying amounts of intrinsic factor in the gastric juice. Strauss and Castle (27) have shown that autolysed yeast is a potent source of the 'extrinsic factor', and wheat germ, although richer in vitamin B_1 than B_2, is probably also a good source. Although the intrinsic factor be scanty, the product according to the mass action of the intrinsic factor and the extrinsic factor might be considerable when the extrinsic factor is given in large quantities. To settle this point, by avoiding interaction with gastric juice, yeast extracts are being administered parenterally, as will be reported later (33).

2. Experiments are in progress to determine whether or not material potent for pernicious anaemia may arise or increase during the autolysis of yeast, perhaps from the activation of 'extrinsic factor' by an enzyme thus liberated from the yeast. The action of the enzyme would be analogous to the role played by the intrinsic factor of normal gastric juice.

3. In addition to extrinsic factor there might exist in yeast, and perhaps in wheat germ, small quantities of a substance resembling the 'liver extract principle'. If this is the case, positive results may be expected from the

parenteral administration of yeast extracts. To test this possibility, yeast has been extracted by the Medical Research Council process used for liver extract and administered orally or parenterally (33).

It will be noted that the principle in Marmite effective in pernicious anaemia is soluble in 65 per cent. alcohol, and is relatively heat-stable, in that it withstands prolonged heating at 86 to 88° C. during the evaporation of the alcohol. Preliminary experiments with yeast fractions have suggested that potency for pernicious anaemia does not run parallel to vitamin B_2 content as tested in rats (33).

Until more evidence is available it is not possible to state definitely to what factor or factors yeast owes its effect in pernicious anaemia, and further discussion of the subject is left for a subsequent paper, which will describe the attempts made, by the oral and parenteral administration of vitamin concentrates and other fractions derived from yeast, to determine the nature of the active principle and its mode of action.

Summary and Conclusions

1. In idiopathic hypochromic anaemias, with or without achlorhydria, and whether or not the diet has been grossly defective, no effect upon haemoglobin regeneration has followed the administration of massive doses of yeast or wheat germ preparations. The possible value of these substances in supplementing the action of small doses of iron is being investigated.

2. The experiments of Parsons suggest that yeast as well as iron may be indicated in the nutritional hypochromic anaemias of pregnancy.

3. In two patients with atypical pernicious anaemia showing an incomplete defect in the secretion of hydrochloric acid combined with a gross dietary deficiency, and associated in one case with dysphagia of the Plummer-Vinson type, the administration of Bemax and Marmite was followed by a haematopoietic response.

4. Of ten cases of classical pernicious anaemia treated with yeast and wheat germ preparations, seven showed a response and three failed to respond. Wheat germ in the form of Bemax gave an uncertain positive result in one case and negative results in two others. Yeast, in the form of Marmite or of an extract derived from Marmite, gave positive results of greater or less degree in six out of seven cases. One case which failed to respond to Marmite failed also to respond to dried yeast (Yestamin).

5. In classical pernicious anaemia, and also in the two cases of atypical pernicious anaemia, the responses were usually less in degree than those obtained from Marmite in certain megalocytic anaemias without achlorhydria which are believed to be due to causes other than defective gastric secretion of the intrinsic factor, namely tropical macrocytic anaemia, and complicating idiopathic steatorrhoea.

6. From the therapeutic point of view the variable and usually sub-

maximal results obtained, with doses as large as can be tolerated, indicated that none of the preparations used is a satisfactory substitute for liver in the relapse stage of pernicious anaemia. On the other hand, the responses so far obtained from a 65 per cent. alcoholic extract of Marmite suggest that an inexpensive product suitable for the treatment of pernicious anaemia may yet be obtained from yeast.

7. The possibility is discussed that yeast preparations may owe their potency in pernicious anaemia to one or more factors: (i) extrinsic factor, (ii) a breakdown product of the extrinsic factor perhaps resulting from the interaction of this substance with an enzyme liberated during the autolysis of yeast, or (iii) a substance resembling the 'liver active principle'.

8. Further discussion is left for a subsequent paper, which will describe attempts made, by the oral and parenteral administration of vitamin concentrates and other fractions derived from yeast, to determine the nature of the active principle and its mode of action.

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XANTHOMATOSIS GENERALISATA OSSIUM [1]

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With Plates 30 to 33

Since Mandl (1) in 1926 proved that extirpation of an adenoma of the parathyroid exercises a curative influence upon von Recklinghausen's disease of the bones the interest in generalized diseases of the skeleton has greatly increased. Whereas formerly cases of these diseases were considered to be of only casual importance, now every case of generalized bone disease is studied for symptoms of hyperparathyroidism. As soon as even slight indications of increased parathyroid function are found an exploration of the parathyroid is deemed necessary. Often the decision to operate is made, even when the symptoms are hardly suggestive of hyperparathyroidism. This is easily understandable because the results of removal of a parathyroid adenoma in cases of typical von Recklinghausen's disease are so convincing (2) that an exploration of the parathyroid would seem to be justified in nearly every case of generalized bone disease. This misconception is supported by the fact that in some cases of von Recklinghausen's disease in which the clinical and biochemical findings of hyperparathyroidism were not characteristic, extirpation of a parathyroid adenoma has led to healing of the bone disease, even when the leading symptom of hypercalcaemia has been absent. Finally, this chapter of parathyroid pathology becomes more complicated, because even when no adenoma of the parathyroid is discovered at operation such a tumour may nevertheless be present. The adenoma is not always found in its typical position i.e. on the posterior wall of the thyroid gland. It may develop from aberrant parathyroid glands in the anterior mediastinum, or even between the oesophagus and the first thoracic vertebra (3). Exceptionally a parathyroid tumour is hidden *in* the thyroid gland (4): these intrathyroidal adenomata of the parathyroid offer exceptional difficulties to the surgeon. Therefore, in a case of suspected von Recklinghausen's disease of the bones, even if no tumour is found at operation the presence of a parathyroid adenoma is not completely excluded. The persistence and patience which the surgeon has to display in these cases are clearly shown by the following history of a patient we were able to study personally (5). (See Table I.)

A girl of 21 years broke her thigh-bone in 1923. Nine weeks after the accident she could walk again. In 1924 she sustained a fracture of the left

[1] Received April 21, 1933.

arm after a slight trauma; this healed in seven weeks. She married in 1927 and in the same year she broke her right arm. In 1930 she had severe pain in both legs. At first she could walk, but from November she had to stay in bed, chiefly because at the end of 1930 she broke both thighs spontaneously. In 1931 X-rays showed that the patient was suffering from von Recklinghausen's disease with multiple cysts in many bones, thinning of the bone cortex and serious deformities of the whole skeleton. In July 1931 analysis of the serum showed considerable hypercalcaemia (14·62 mg. per cent.). She was operated upon in the same month. The left inferior parathyroid seemed to be increased in size and measured 6 mm. × 1 cm. The extirpation of this small tumour, however, did not change the condition at all; the pains and hypercalcaemia persisted. In September 1931 at a second operation, a small nodule, taken to be parathyroid, was removed. Microscopical examination showed it to be normal thyroid tissue.

After the second operation the course of the disease was progressive. New cysts appeared, for instance in the mandible. Her general condition became worse, she had no appetite. She became emaciated and had persistent hypercalcaemia. Therefore in December 1931 a third operation was performed and an adenoma of the parathyroid was found behind the thyroid in a duplication of the capsule. The tumour was the size of a cherry. Immediately afterwards the serum calcium fell to the normal value, the pains disappeared, and, after a few months, the patient was able to sit up in bed.

TABLE I

Clém. W., 29 years. von Recklinghausen's disease.

	Serum Ca mg. %	Ultrafiltrable Calcium mg. %
8.6.1931	14·62	6·62
22.6.1931	Extirp. small parathyr. adenoma	
20.7.1931	15·37	—
28.7.1931	12·73	—
30.7.1931	13·47	—
22.9.1931	New operation, nothing found	
19.10.1931	15·17	—
15.12.1931	Third operation, extirp. adenoma parathyr. (cherry)	—
17.1.1932	9·01	5·00
22.1.1932	9·95	—
11.2.1932	9·80	—
9.7.1932	10·73	—

These facts enhance the importance of the differential diagnosis of generalized diseases of the bones. Under the diseases which may easily be mistaken for von Recklinghausen's disease generalized xanthomatosis of the bones must be taken into consideration. Xanthomata are yellow 'tumours' consisting of extensive deposits of lipoids and full of big swollen foam-cells. The name tumour is incorrect, because a xanthoma consists of granulation tissue: therefore it is often called a 'lipoid-granuloma' (6). One well-known clinical picture is caused by xanthomatosis of the bones, namely, Schüller-Christian disease (7), in which the xanthomatosis is localized in the

bones of the skull. Usually when xanthomatosis of the bones is discussed attention is only given to this specific localization of the xanthomatous degeneration in the skeleton of the skull. In Schüller-Christian's disease, which some investigators prefer to call Hand's disease (8), the following features are observed: (1) Multiple erosions of the bones of the skull. (2) Exophthalmos, usually bilateral. (3) Diabetes insipidus. (4) Often infantilism and retardation of growth of the patients, who are, in the majority of cases, children.

It has been proved that all these symptoms are caused by a xanthomatous degeneration of the bone. The holes in the skull are filled with xanthomatous tissue. The bony wall of the orbit is destroyed by xanthomatous masses, causing the exophthalmos; and the xanthomatous degeneration of the hypophysis and adjacent parts (tuber cinereum) account for the diabetes insipidus and the infantilism. Not seldom dystrophia adiposogenitalis, also depending upon the lesions in the neighbourhood of the hypophysis, is observed in these cases. Patients with Schüller-Christian's disease may have other manifestations which are not so constant as the four symptoms mentioned above. Decay of the teeth, for example, is caused by xanthomatosis of the maxilla and the mandible; deafness by degeneration of the petrous portion of the temporal bone: dyspnoea by masses of xanthomatous cells deposited in the lungs and so on.

The close connexion between the symptoms of Schüller-Christian's disease and xanthoma tuberosum was demonstrated by Wiedmann and Freeman (9) who were able to perform an autopsy on the patient described by Griffith (10) with the symptoms of Schüller-Christian's disease, complicated by xanthomatosis tuberosum of the skin and liver. Strangely enough, such a combination is only rarely observed.

Clinicians distinguish: xanthomatosis of the skin, of the internal organs (liver, spleen, kidney) and of the bones. It is remarkable that combinations of these three categories of xanthomatosis are but infrequently observed, though Hertzenberg (11) found a xanthomatous lesion in the liver in her case of Schüller-Christian's disease. Chiari (12) mentions very discrete lesions in the renal pelvis, and Hochstetter and Veit (13) found a xanthomatous tumour at the hilum of the kidney. In 1928 Rowland (14) found, in a typical case of Schüller-Christian's disease without any lesion of the internal organs, that the holes in the skull, the exophthalmos, and the diabetes insipidus were caused by xanthomatous degeneration of the bones and the hypophysis. He defined the histological lesions as masses of xanthomatous cells consisting of proliferated and swollen reticulo-endothelial cells, loaded with cholesterol, giving the appearance of foam cells.

The interest in these cases is increased because the lesions may disappear spontaneously. In several cases X-ray treatment, first applied by Sosman (15), seems to have had a curative influence. Often, however, it has been observed, that simultaneously with the disappearance of certain lesions of the skull under X-ray or radium-treatment (16) fresh perforations of the cranium have developed: the beneficial influence of Röntgen treatment is

only local and not general. The disease is a serious one because one-third of the forty-five cases which Sosman could collect from the literature in 1932 had ended fatally. Moreau (17), who found thirty-four cases in the literature, mentioned that nine of these were cured. Of twenty-four young children (2–4½ years) five had died and seven recovered: of these last cases five cleared up without treatment, two only after X-ray treatment. Of all the thirty-four cases he found in the literature nine were healed and ten had died.

There is no reason why xanthomatosis generalisata ossium should be limited only to the bones of the skull. As a matter of fact several cases of Schüller-Christian's disease have been reported where similar lesions were present in other bones in addition to the classical cranial lesions. In Hertzenberg's case xanthomatous tissue was also present in the vertebrae and femora. In Höfer's case (18) Schilling found abnormal cells in the bone-marrow which he considered to be xanthomatous; in Moreau's case there was a big loss of bone substance with polycystic appearance of the left iliac bone (19). One year afterwards this defect was nearly completely filled up by intensely calcified tissue, but after another year a new hole had developed in this calcified bone scar. The same case showed a large bone defect in the right femur which had also disappeared completely after one year. After another year, however, new osteoporotic defects had developed in the same bone.

The patient of Pende (20), Barco (21), and Cignolini (22), a boy of 15 years old, had large bone lesions in the upper parts of both femurs, and suffered a spontaneous fracture of the right femur which healed in normal time. Alberti (23) described a man, 21 years of age, with the typical symptoms of Schüller-Christian's disease and, in addition multiple foci of absorption of bone. In both humeri and femora these osteoporotic cyst-like defects increased in intensity before death. Perhaps the case of Schultz, Wermbter and Puhl (24) may also be included in this group of cases of Schüller-Christian's disease with lesions of other bones in addition to those of the skull. These authors described a definite case of Schüller-Christian's disease under the name of 'réticulo-endotheliose generalisée'. Here also the marrow of the tubular bones was packed with the abnormal cells.

Schüller-Christian's disease should therefore be designated the cranio-hypophyseal localization of xanthomatosis of the bones. Perhaps it would be better to call it, not xanthomatosis, but cholesterol lipoid-granulomatosis. Xanthomatosis, or lipoid granulomatosis; includes all sorts of lipoid degeneration, whereas the lipoid in Schüller-Christian's disease consists of cholesterol. Because in typical cases of Schüller-Christian's disease visceral organs may be affected (liver, lungs, kidney) and extensive lesions of other bones have been described, the possibility or even the probability exists that xanthomatosis of the bones may exist without localization in the skull and the hypophysis. There must be cases where all the typical symptoms of Schüller-Christian's disease are absent, but where the cholesterol degeneration

with foam cells is limited to other bones than the skull. These cases must form a source of error in the differential diagnosis of generalized bone diseases because the X-rays of the xanthomatous lesions of the long bones in Schüller-Christian's disease, as published by Alberti, Barco, and Moreau show a great similarity to those of von Recklinghausen's disease. This can easily be understood if one remembers that histologically xanthomatosis of the bones is a real lipoid granulomatosis: fibrous granulomatous tissue full of foam cells and cholesterol invades the bone. Extensive fibrosis of the bone-marrow and of the Haversian canals with absorption of bone results by which the similarity of the radiograms of xanthomatosis and of von Recklinghausen's osteitis fibrosa generalisata is explained. Cases of *extensive* generalized xanthomatosis or cholesterol lipoid-granulomatosis of the bones without cranio-hypophyseal localization must therefore from time to time be confounded with von Recklinghausen's disease.

Before going into this problem it is important to remember that *local* xanthomatous degeneration of one bone only has been described, although the number of cases is small. The last case was reported by Schröder (25) in which a central xanthomatous giant cell tumour of the distal part of the left fibula was extirpated seven years after the first symptom had been observed by the patient. Some years earlier the tumour after a biopsy had been diagnosed as melanosarcoma, but fortunately the patient had refused amputation. A diagnosis of osteitis fibrosa made before the ultimate operation was partly confirmed by the histological examination. The tumour was described by the pathologist as osteitis fibrosa with accumulations of foam cells full of cholesterol deposits. It had the same structure as the well known and not infrequent xanthomata of tendon sheaths and joint capsules. The cholesterol content of the serum of this patient was 231 mg. per cent.

Schröder cites other analogous cases: Mervill found multiple xanthomatous lesions in the bones of the fingers, Vermooten xanthomatosis of the terminal phalanx of the thumb eroding through the cortex, Krogius a xanthomatosis of the medial condyle of the left femur, Zeyland and Dega a xanthomatous tumour of the lower part of the femur. Here Chester's investigation has to be mentioned. Chester (6) found accidentally at an autopsy on a man of 44 years an extensive lipoid granuloma of the femur with osteoplastic reaction around the lesion. This was the reason why Chester examined all the bodies of patients with xanthelasma of the eyelids for the presence of lipoid granulomatosis of the bones with a positive result in only one case. In a man of 69 years with xanthelasma he found a big lipoid granuloma of the femur and another in the tibia.

By the scarcity of the published cases it is clearly shown that localized xanthomatosis of the bones is infrequent, especially when compared with the number of cases of xanthomatosis of the tendon sheaths which one may observe in surgical practice. The significance of localized xanthoma of the bones in the elucidation of the problem of generalized xanthomatosis of

the bones seems doubtful if one draws the following comparison. Localized or focal osteitis fibrosa cannot be distinguished histologically from von Recklinghausen's generalized osteitis fibrosa. Nevertheless, the etiology of localized osteitis fibrosa has nothing to do with the parathyroids.

We now return to generalized xanthomatosis of the bones without symptoms of Schüller-Christian's disease. The difficulties in the differential diagnosis between general xanthomatosis of the bones and generalized osteitis fibrosa cystica (von Recklinghausen's disease) were revealed by a publication of Kienböck, the famous Viennese radiologist, whose work on bone diseases has become classical. In 1932 he published, together with Meworach (26), the history of a patient who showed an extensive cystic degeneration in the upper part of the right femur with a spontaneous fracture. Four dorsal vertebrae also showed cystic foci. Originally Kienböck thought that the patient was suffering from osteitis fibrosa cystica. However, the swelling of the femur was much smaller than one would expect in a case of advanced von Recklinghausen's disease. Five months afterwards a swelling of the tenth rib appeared. This piece of bone was resected. The nature of the granulomatous tissue of the resected rib remained uncertain until Maresch made the diagnosis of lipoid-granulomatosis. Here was a case of multiple cystic foci giving the impression of von Reckinghausen's disease at X-ray examination and nevertheless caused by multiple xanthomatous lesions. This case of Kienböck enabled us to make the correct diagnosis of the following patient,[2] a girl of 10 years.

Record of Case

This girl has no family history of any importance. When she was 7 years of age menstruation started and symptoms of puberty developed. Mentally, however, she was very backward, even after allowing for the fact that from the age of 7 she had to spend long periods in hospitals; thus it was remarkable that she did not know where she lived and that she hardly remembered things which have happened to her. When she was 7 years old she fell and broke her femur. During the following two years she had five fractures of both femurs; one was a spontaneous fracture which occurred when she turned over in her bed. After a course of treatment with calcium injections and ultra-violet rays she improved so much that she could walk again and had no more fractures.

General examination at the age of 10 years did not show anything abnormal. The urine was normal. Spleen not palpable; there is no record of the blood picture. The Wassermann reaction was negative. The basal metabolic rate was normal. On the skin of the face and the chest were several small brown naevi.

[2] This case has already been described in brief by one of us (Parisel, Ch., 'A propos d'un cas de maladie de Recklinghausen: Rectification du diagnostic; Xanthomatose généralisée.' *Bull. et mém. de la Soc. Belge d'Orthopédie*, Tome iv. 6, 1932.

There were gross deformities of the upper parts of both femurs, evidently caused by fractures. One of the legs was shorter than the other, which explained the difficulty in walking. Palpation showed that the right humerus was swollen. There was no pain during palpation of the diseased bones. X-rays showed in both femurs extensive osteoporotic lesions, giving the appearance of multiple cysts. Many of the other long bones were also affected. The most extensive lesion was in the right humerus, where a large focus of degeneration of the bone was present. The cortex had almost disappeared at these sites. The calcium content of the blood-serum was at first found to be 12·6 mg. per cent.

The diagnosis of von Recklinghausen's disease was made, and the girl was operated upon twice, but no parathyroid adenoma was found, despite the fact that the second operation was an extensive exploration of the neck by a surgeon with experience in parathyroid surgery.

When we saw this patient together there were certain points against the diagnosis of von Recklinghausen's disease with hyperparathyroidism.

1. Absence of hypercalcaemia is always an argument against hyperparathyroidism, although it cannot be denied that in a few cases where an adenoma of the parathyroid was found at operation the calcium content of the serum had been found to be normal (27). However, such is the exception, and hypercalcaemia, even if not absolutely necessary for the diagnosis, must be considered as one of the most convincing manifestations of von Recklinghausen's disease.

2. Most patients with von Recklinghausen's disease suffer a good deal of pain. In the severest cases nursing of the patients becomes extremely difficult, because even the slightest active or passive movement causes excruciating pain. Neither spontaneously nor with firm pressure on the diseased bone did our patient have any pain at all.

3. In most cases of von Recklinghausen's disease there is thinning of the cortex, and the diseased part is usually swollen. Usually, too, in the affected parts some structures in the form of bone septa remain visible. In our case there was only moderate swelling of the affected bones, more marked in the humerus and the tibia, and septa were nowhere visible. On the contrary, the lesion showed itself on the X-ray as an even patch.

Influenced by the publication of Kienböck and Meworach on the difficulty in distinguishing xanthomatous bone lesions from osteitis fibrosa cystica generalisata, we thought that our case might be one of xanthomatosis generalisata. However, none of the following classical symptoms of Schüller-Christian's disease were present. (1) In the skull no defect could be found by palpation or X-ray. On the radiogram the impressiones digitatae were somewhat too deep, but there were none of the well-known round defects of this disease. (2) No evidence of diabetes insipidus and no röntgenological deformity in the sella turcica could be found. (3) There was no exophthalmos. (4) The development of the girl was quite normal; there was no question of impaired growth or infantilism.

Therefore, if xanthomatosis of the bones was present in our case, the most typical localization of this disease, i.e. the cranio-hypophyseal lesions, were absent.

In some cases of Schüller-Christian's disease hypercholesterolaemia has been found. It is, however, not a constant feature, and it is evidently only present during the active phases of the disease. In our case the total cholesterol content of the blood, taken on July 16, 1932, was 322 mg. per cent. The lecithin content of the same blood was 220 mg. per cent. This definite hypercholesterolaemia was certainly a strong argument for the possible diagnosis of xanthomatosis. A new biopsy in the subtrochanteric region of the femur was performed. The curette did not break into a cavity: evidently no cysts were present, although the X-rays had seemed to indicate the presence of cystic lesions. Only extremely soft and friable bone tissue was found. It was easy to obtain several small fragments of bone with the curette, which were fixed in Dustin's fluid.[3] Prof. W. M. de Vries, the pathologist of the University of Amsterdam, examined the material. He wrote the following report:

'Tissue scraped out from affected area of bone.

Macroscopically. Four pieces of tissue, together weighing about 2½ grm., fixed in a green fluid, smelling of vinegar.

The surface is somewhat rough, pale green, with brown flecks due to blood; the section looks like fine spongy bone tissue; the tissue is easily cut with the knife; the section is similarly pale green, with here and there darker flecks.

Microscopically. Blocks were made for ice- and paraffin-sections. First, a little was scraped off from the section and the scraping examined in glycerine; one recognizes fibrous tissue and small particles of bony tissue; with the polarizing apparatus one sees in the bony and fibrous tissue some double refraction; but in addition one sees a few groups of strongly double-refracting particles, small and irregular, both round and long; no clearly double-refracting drops; after warming the preparation in these places, one sees clearly double-refracting drops with dark crosses.

The section shows small columns, usually not connected, lying in a fibrous tissue moderately rich in cells. The bony columns have mostly an osteoid border, and often show lacunar absorption with osteoclasts here and there. The picture is compatible, therefore, with osteitis fibrosa.

Nevertheless, one finds here and there, sometimes along a vessel, a group of foam cells and also sometimes a few foam cells in the fibrous tissue. In the Sudan sections there are lying in these places many double-refracting fat particles, and there is more lipoid than one would have thought from the haematoxyl-eosine sections; and it looks as though there were also particles in the fibrous tissue outside the cells.

In one part there is but little or no lipoid; in another part more.

The affection looks, therefore, like Schüller-Christian's disease; the paraffin sections give the same picture, but there are somewhat fewer foam cells.'

His examination, therefore, proved clearly that the bone showed signs of osteitis fibrosa, but at the same time in the fibrous tissue there were great accumulations of foam cells loaded with double-refracting lipoids and fats.

[3] Pure formol 20 c.c.; chromic acid 8 per cent. 75 c.c.; glacial acetic acid 5 c.c.

The microscopical sections showed the typical picture of xanthomatosis of the bones in the form of a lipoid granulomatosis. The same tissue has been found in Schüller-Christian's disease of the skull. Therefore our patient must have been suffering from generalisata xanthomatosis of the bone *without* the typical localization in the skull or in the hypophysis.

This patient had apparently arrived at a non-active stage, because all the analyses of the serum which we made afterwards never again showed a definite hypercholesterolaemia. Thus we found:

1932.	Total cholest.	Free cholest.	Cholest. esters	Lecithin.
Aug. 13	197 mg. %	—	—	190 mg. %
Oct. 19	181 „	39 mg. %	142 mg. %	151 „
Nov. 10	194 „	28 „	166 „	184 „

We tried to show the abnormality of the cholesterol metabolism in still another way, which has been pointed out by Bürger and his collaborators. Bürger (28) writes that after ingestion of 5 gr. cholesterol dissolved in 50–100 gr. olive oil, given on an empty stomach, the cholesterol content of the serum of normal people is increased, and may reach, four hours after the ingestion of the cholesterol, a level twice as high as before. On the contrary, in a case of xanthomatosis of the skin, he found a decrease of the cholesterolaemia after ingestion of cholesterol. We tried this test on our patient, but gave 4 gr. cholesterol because the girl was only 14 years old. The cholesterol content of the serum was not raised after the administration of cholesterol.

	Total cholest.	Free cholest.	Cholest. esters	Lecithin.
Before cholest.	194 mg. %	28 mg. %	166 mg. %	184 mg. %
4 hours after	179 „	33 „	146 „	236 „
8 hours after	189 „	23 „	166 „	261 „

However, we do not attach too much importance to this 'functional test of cholesterol metabolism' because several control cases with normal and abnormal cholesterol metabolism did not show increase of cholesterolaemia after taking 4 gr. of cholesterol in olive oil. All the analyses were performed by Windaus's gravimetric method.

		Total chol.	Free chol.	Chol. esters	Lecithin.
Sn. 15 y.	Before cholest.	166 mg. %	55 mg. %	111 mg. %	—
Mitral	4 hours after	181 „	63 „	118 „	—
Regurgitation	8 hours after	168 „	55 „	113 „	—
Sch. 12 y.	Before cholest.	214 „	71 „	143 „	141 mg. %
Pleurisy	4 hours after	228 „	67 „	161 „	126 „
—	8 hours after	244 „	69 „	175 „	183 „
Jes. 14 y.	Before cholest.	221 „	60 „	161 „	—
Anaphylactic	4 hours after	214 „	66 „	158 „	—
Purpura	8 hours after	213 „	63 „	150 „	—
Kl. 49 y.	Before cholest.	166 „	51 „	115 „	—
Cirrhosis of liver	4 hours after	171 „	43 „	129 „	—
—	8 hours after	178 „	65 „	114 „	—
St. 17 y.	Before cholest.	125 „	30 „	95 „	—
Polyarthritis?	4 hours after	116 „	29 „	87 „	—
—	8 hours after	121 „	40 „	81 „	—
Hoy. 32 y.	Before cholest.	732 „	197 „	535 „	361 mg. %
Xanthomatosis	4 hours after	710 „	230 „	480 „	384 „
of the skin	8 hours after	747 „	185 „	562 „	384 „

If one compares the values obtained in our patient with xanthomatosis of the bones with those in the other patients, the only difference seems to be that there is a relative excess of cholesterol esters over the free cholesterol. Usually 60 to 70 per cent. of the total cholesterol is formed by the esters, 30 to 40 per cent. by free cholesterol, but in our case of xanthomatosis of the bones more than 80 per cent. of the total cholesterol was formed by the esters. This would agree well with the results of Epstein and Lorenz (29), who found that in the lesions of Schüller-Christian's disease the amount of cholesterol esters is nearly five times greater than that of free cholesterol. In the case of generalized xanthomatosis cutis, which is mentioned here, the relation of cholesterol esters is also rather high. However, in another case of xanthomatosis of the skin, complicated by a retro-orbital xanthoma, the free cholesterol was 216 mg. per cent., the cholesterol esters 293 mg. per cent., making a total cholesterol content of 509 mg. per cent.

The biopsy of our case has conclusively proved the diagnosis of generalized xanthomatosis. Probably these cases are not too frequent. They have to be looked for, especially in patients who have been considered to be cases of von Recklinghausen's disease on the evidence of the radiograms, but in whom no parathyroid adenoma was found at operation. In a few of these cases the radiograms published with the text seem to point to the presence of xanthomatosis. Recently Kienböck and Schneck (30) had an analogous experience. A woman of 26 years suffered a fracture of the right humerus in 1927. X-rays showed the fracture, but in addition the whole humerus was destroyed by multiple central cysts. The cortex was thin and the surface of the bone smooth. Both epiphyses were normal. In 1928 cysts were also found in the right and left femurs. A diagnosis of von Recklinghausen's disease was made, but operation in 1930 failed to reveal a parathyroid adenoma. On March 12, 1932, there was a fresh fracture of the right humerus in the same place as that of five years before. At this time the diagnosis was changed to generalized xanthomatosis of the bones for the following reasons. (1) The lesions were not accompanied by marked swelling of the bones. (2) The lesions had a bilateral symmetrical distribution. (3) No complications had arisen during the interval of several years, and the general condition was excellent.

This case of Kienböck and Schneck agrees in many respects with the findings in our case, but their diagnosis has not yet been confirmed by any direct evidence.

Conclusion

There exists a generalized xanthomatosis of the bones without any symptoms of Schüller-Christian's disease, i.e. without cranio-hypophyseal localization. The radiograms of the osteoporotic lesions of generalized xanthomatosis of the bones may easily be confused with von Recklinghausen's disease of the bones (osteitis fibrosa generalisata).

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FIG. 1. Extensive destruction in head and neck of the femur with formation of pseudo-cysts

FIG. 2. Left humerus showing a pseudo-cyst in the shaft

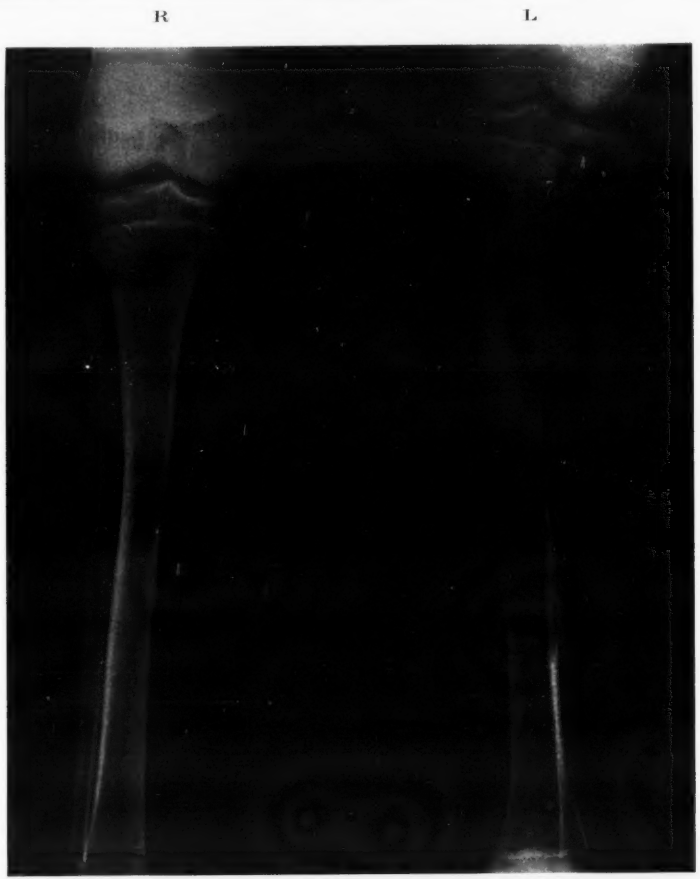

FIG. 3. Right and left tibia and fibula. The shaft of left tibia is almost decalcified. Diffuse swelling of the bone.

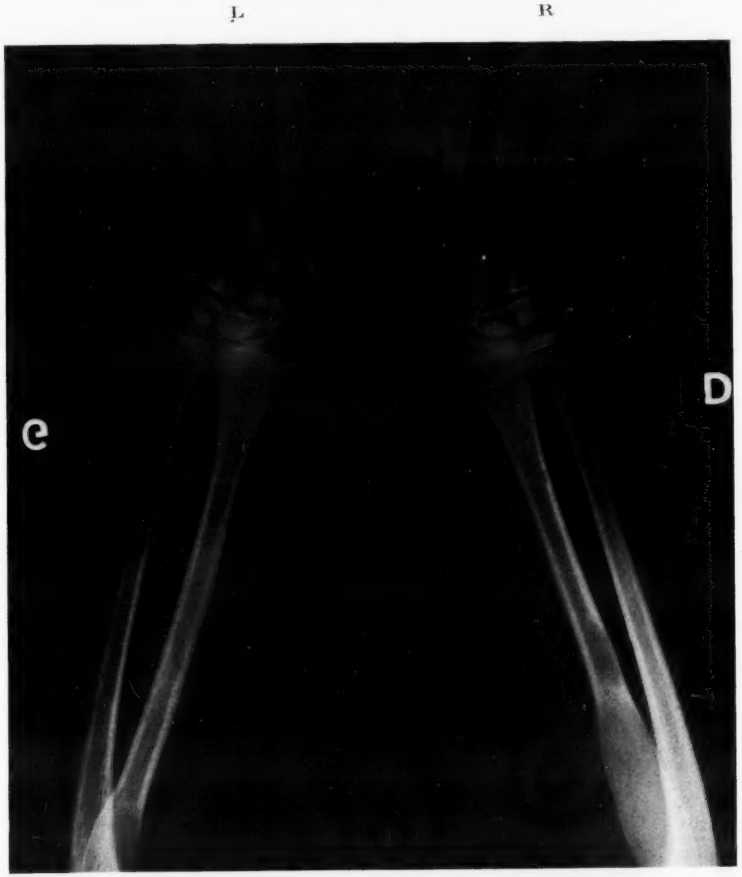

FIG. 4. Left and right radius, ulna, and hand. There is a diffuse swelling of the upper part of the right radius where the bone calcification is very deficient by absorption of the shaft. The right first metacarpal is swollen and the second and third metacarpals on the left show patchy foci.

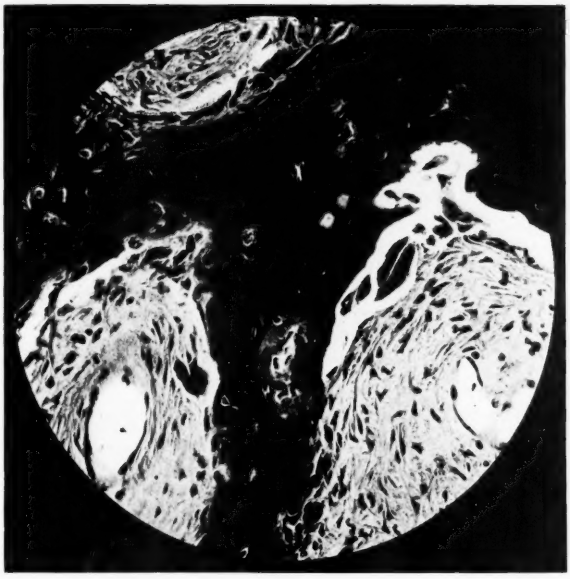

FIG. 5. Calcified bone trabecula surrounded by fibrous bone marrow. Some osteoclasts situated at the margin of the bone. Magnification 250 ×

FIG. 6. The lower part of the preparation shows a darkly stained bone trabecula; the rest of the tissue is fibrous bone marrow with a few blood vessels. In the centre are small nests of foam cells (Lipoid ceils). Magnification 120 ×

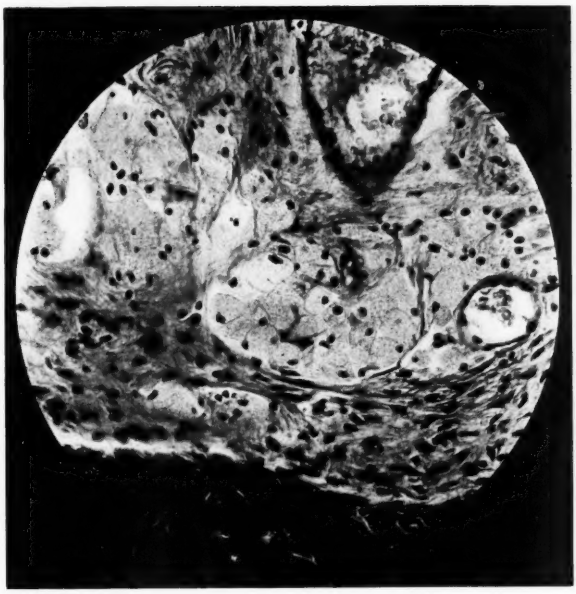

FIG. 7. Lipoid cells of the same preparation.
Magnification 250 ×

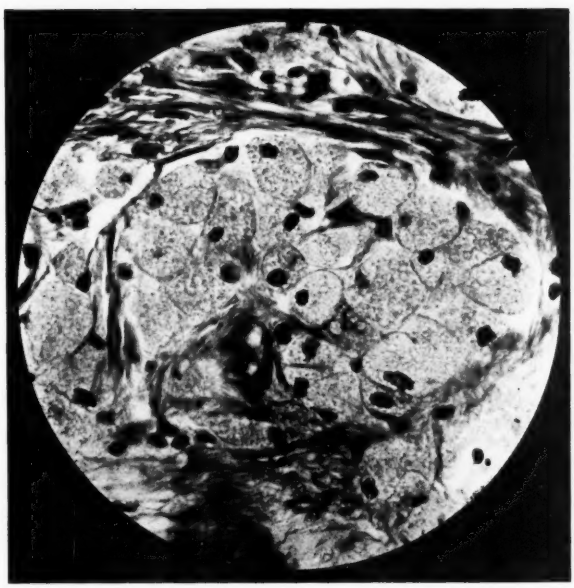

FIG. 8. Central groups of lipoid cells. Magnification 480 ×.
Note the clear-cut foam structure of the bigger cells with the darkly stained nucleus

616.853
616.121

ACID-BASE EQUILIBRIUM OF BLOOD IN EPILEPSY [1]

By FRANCIS LEO McLAUGHLIN and RICHARD HENRY HURST

(From the Central Pathological Laboratory of the London County Mental Hospitals)

In epilepsy much attention has been directed to metabolic changes which influence the incidence of seizures. It has been demonstrated that in certain cases seizures may be modified by measures which affect the acid-base balance of the organism, induced alkalinity favouring the number and severity of seizures, and induced acidity having the reverse effect. In view of these observations, many attempts have been made to find a correlation between the physical condition of epileptics and a disturbance in the regulation of acid-base equilibrium of the blood.

It has been established by most authors that in the interval period between fits, variations in blood constituents are usually within physiological limits. At the time of the actual seizure, however, much confusion prevails as to what takes place. Some authors, for example, claim that the fit is preceded by an increase of alkali reserve (alkalosis) and of pH (alkalaemia), others that the reverse (acidosis and acidaemia) takes place, while yet others have observed no appreciable change. The explanation of these diverse opinions lies in the fact that the normal variation in alkali reserve and pH of different individuals, and even of the same individuals at different periods is of wide range, and it follows that sound conclusions can be drawn only as a result of a large number of observations. The difficulty of obtaining a large number of cases during and particularly preceding seizures is apparent. It appeared to us, therefore, that the most satisfactory way of approaching the problem was to attempt to obtain specimens of blood from individuals immediately before, during, and after a particular seizure and to compare these with samples taken during the intervals between fits.

The clinical material selected for this study consisted of institutional cases of essential or idiopathic epilepsy, whose fits were of frequent occurrence. The administration of drugs was discontinued and careful observations made for twenty-four hours before specimens were taken. Notes were made during this period of all possible modifying factors, such as diet and previous medication, the mental and motor states of each patient, and the time and character of any sensations, aura, or fits. Samples of venous blood were

[1] Received April 24, 1933.

taken from several patients at frequent intervals for a short time in the expectation that one of them might have a seizure shortly after a vene-puncture. If this occurred, further punctures were made during and after the convulsive crisis. This procedure was successful on very few occasions, since the probability of a seizure taking place during the period of observation was slight. On the other hand, a number of specimens was obtained, representative of various inter-seizure periods.

A series of normal controls was obtained and this was supplemented by healthy, high-grade defectives employed as ward workers in the mental institutions. The advantage of including these patients was that control specimens were thereby obtained under conditions identical with those of the epileptics and could be analysed at the same time.

All subjects at the time of blood-sampling were in the post-absorptive state and were either in bed or had rested for at least one hour.

Experimental

Vene-punctures, usually of the median basilic vein, were made without stasis, the blood being collected under paraffin in an air-tight syringe and run immediately into tubes containing paraffin and a small amount of Evans's 9 : 1 mixture of potassium oxalate and sodium fluoride, previously moistened with two drops of saline. The blood was stirred gently with a thin glass rod and the tubes were then stoppered and placed in an ice-box. The blood samples were allowed to stand in a refrigerator until sufficient plasma had separated out to be removed, under paraffin, without centrifuging. In this way, any possible loss of CO_2 was minimized.

Estimations of 'alkali reserve', pH and lactic acid were carried out on the plasma.

Alkali reserve was determined by the titrimetric method of van Slyke.

pH measurements were made by means of the glass electrode outfit of Kerridge (13). The precise technique adopted was that described by one of us (Hurst (10)).

Lactic acid was determined by the method of Friedemann, Cotonio, and Shaffer (6), modified by Friedemann and Kendall (7). The percentage recovery of lactic acid was between 95 and 98.

The results obtained fall into two sections:

1. General statistical results, consisting of averages of a number of isolated samples; these are shown in Tables I–III.

2. Results from successive vene-punctures performed on individual cases before, during, and after a fit; these are represented graphically in Figures 1–3.

Discussion

1. *General statistical results. Alkali reserve.* Divergent opinions have been expressed with regard to the alkali reserve content of the blood in epilepsy and its variation in relation to seizures.

Bigwood (2), in presenting a large amount of experimental evidence, concluded that in the interval period between fits the blood bicarbonate rested within normal limits. Katzenelbogen (12) reported that the 'interval' alkali reserve was within the normal limits of 54–74 volumes CO_2 per cent. in thirty-one patients, and Lennox and Allen (14) found the plasma bicarbonate within 55 and 70 volumes CO_2 per cent. in eighty-eight out of 100 patients. Ballif and Reznic (1) state that the alkali reserve was normal in the interval periods and immediately before seizures, but fell after seizures.

Gozzano (9), however, found that in one-third of his cases the 'interval' alkali reserve was higher than normal. Dautrebande (4) also noted an increased alkali reserve, but stated that this had no relation to the occurrence of fits.

Torres Lopez (19), on the other hand, found that the 'interval' alkali reserve was normal in the majority, but diminished in about 30 per cent. of his cases. Villacián and Urra (20) report a diminished alkali reserve in the period preceding the fit. Puca (17) also found a lowered alkali reserve in the pre-paroxysmal phase with further lowering in the period following the attack.

Di Renzo (5) presented findings which differed from those of the above authors and suggested that the alkali reserve rose from the normal value twenty-four hours before the fit, reached a maximum a few minutes before the crisis, fell rapidly to the normal value immediately before, and remained normal during and after the fit. The results tabulated, however, particularly for the period immediately preceding the fit, are too few for detailed critical examination.

The results obtained for alkali reserve in the present investigation are recorded in Table I.

These show, firstly, that the alkali reserves of epileptics in the interval period fall, with very few exceptions, within normal limits. Secondly, the average for epileptics of 68·7 vols. per cent., compared with 64·4 vols. per cent. for normals, indicates an increase in epilepsy. This, however, is regarded as merely suggestive, in view both of the wide variation in individual alkali reserves and also of the fact that these patients have been subjected to courses of luminal and other drugs which might conceivably affect their blood alkali reserve content. Thirdly, there is no appreciable difference between the alkali reserves of epileptics in the interval period and those in the two-hour period preceding the fit. It should be pointed out that in the results tabulated for the latter period, we did not include any case in which previous fits had occurred on the same day.

The period of the few minutes preceding the fit is of great importance, but our results are too few to warrant special treatment of this phase. It is clear, however, that there is a fall in alkali reserve during a fit, and by correlating clinical findings with our results it was manifest that the degree of this fall was related to the severity of the convulsion. In cases of severe major fits the decrease in alkali reserve was continued for some minutes

after the crisis, but even in these instances recovery to normal was usually completed within two hours.

TABLE I

Alkali Reserves of Venous Blood-plasma Vols. % CO_2

Case no.	Interval period.		2-hour pre-fit period.		During fit.		0–½ hour after fit.		½–2 hours after fit.	
	No. of obs.	Averages of A. R.	No. of obs.	Averages of A. R.	No. of obs.	Averages of A. R.	No. of obs.	Averages of A. R.	No. of obs.	Averages of A. R.
1a	3	68·5	—	—	2	55	—	—	—	—
1b	7	70·5	—	—	—	—	—	—	—	—
1c	4	72·5	—	—	1	55	2	49	1	70
2	4	72	—	—	—	—	—	—	—	—
3	1	74	—	—	1	64·5	—	—	—	—
4	7	63·5	3	64·5	—	—	—	—	—	—
5	10	65·5	—	—	—	—	—	—	—	—
6	2	70	—	—	—	—	—	—	—	—
7	4	72	—	—	—	—	—	—	2	72·5
8	7	70·5	5	71	2	61	2	69·5	2	70
9	2	70	—	—	1	49·5	—	—	—	—
10	5	70	3	69·5	1	68	4	69	3	70·5
11	3	71	—	—	1	60	1	62	1	62
12	2	70·5	6	70	1	65·5	2	65·5	—	—
13	1	63	—	—	—	—	1	57	—	—
14	3	61·5	1	59·5	—	—	1	57·5	3	59
15	2	73	—	—	—	—	—	—	1	59·5
16	3	65	—	—	1	61·5	—	—	2	64·5
Mean	70	*68·7*	18	*68·8*	11	*59·7*	13	*63·3*	15	*66·3*
Highest individual result	—	78	—	74	—	68	—	71	—	73·5
Lowest individual result	—	58·5	—	59·5	—	49·5	—	44	—	57
Controls.										
Highest	—	73								
Lowest	—	57								
Mean	12	*64·4*								

pH. In contrast with the varied opinions concerning the levels of alkali reserve during epilepsy, there is comparative unanimity amongst authors with regard to the hydrogen-ion concentration of the blood-plasma. It should be noted that previous investigators have employed colorimetric methods for the determination of pH and that these give higher results than those obtained by the glass electrode electrometric technique.

Jarløv (11) found that the blood of epileptics showed a tendency to increased alkalinity before the convulsive crisis and that this was replaced by a decrease following the attack. The attack was regarded as being a defence reaction of the organism against alkaline intoxication. Geyelin (8) concluded that although there was no definite pH curve characteristic of epilepsy, these patients showed a wider daily range than did normals. Osnato and co-workers (15) found that the pH of the plasma in twenty-nine cases was in the normal range, given as 7·33–7·44. Bigwood (2) reported

an increased blood alkalinity preceding seizures and applied the equation of Rona and Takahashi (18), $Ca^{++} = K \cdot \frac{[H^+]}{[HCO_3']}$, to his results, concluding that the effect of increased pH (in the absence of a corresponding decrease in HCO_3'-ions) was a reduction in Ca-ions, which in turn precipitated the fit. Dautrebande (4) suggested that the high pH values obtained were due to the presence in the blood of epileptics of an alkaline substance which combines with difficulty with CO_2 *in vivo*.

TABLE II

pH of Venous Blood-plasma

	Controls.	Epileptics.				
		More than 2 hours before or after fit.	Within 2 hours before fit.	During fit.	0–½ hour after fit.	½–2 hours after fit.
Number of observations	6	20	8	7	11	9
Highest	7·36	7·39	7·42	7·37	7·38	7·40
Lowest	7·30	7·30	7·32	7·15	7·28	7·31
Average	7·32	7·35	7·355	7·29	7·34	7·36

The results recorded in Table II indicate a larger variation between the pH values of epileptics than exists in the normal. To the six normals considered here might be added twelve discussed in a previous paper by Hurst (loc. cit.), all of whom showed pH values lying within the limits for normals given in this table. The average pH in the two-hour period preceding the fit shows no significant rise from that in the interval period. On the average, however, epileptic plasma tends to be slightly more alkaline than the normal, although, as in the case of alkali reserves, this is quite insignificant when applied to individual cases. During the fit there is a fall in pH, the extent of this being dependent on the severity of the seizure and also on the time after the commencement of the fit that the vene-puncture is made. In all cases the pH returns to normal limits in a short space of time.

Lactic acid. Very few determinations of blood lactic acid in epilepsy have been made by previous workers. Osnato and co-workers (loc. cit.) found lactic acid values above normal for epileptics, and state that this increase bears no relation to the time elapsing since the previous seizure, and therefore is not due to the muscular exertion during convulsions. The figures recorded, however, are unreasonably high in a number of cases, and it is very unlikely that they would be obtained with the more refined experimental technique now available for determining lactic acid. Moreover, no experimental results for normal blood-lactic acid are given. Ballif and Reznic (loc. cit.) argue, without presenting experimental evidence, that the fall in alkali reserve immediately after a fit is due to the production of lactic acid resulting from muscular contractions during the seizure.

The results recorded in Table III indicate that in the interval period

between fits the lactic acid content of the blood-plasma of epileptics is normal. This contradicts the findings of Osnato.

TABLE III

Lactic Acid of Venous Blood-plasma (Mg./100 c.c.)

	Controls.	Epileptics (During interval period.)
Number of observations	8	8
Highest	18	18
Lowest	10	10
Average	13·5	13·0

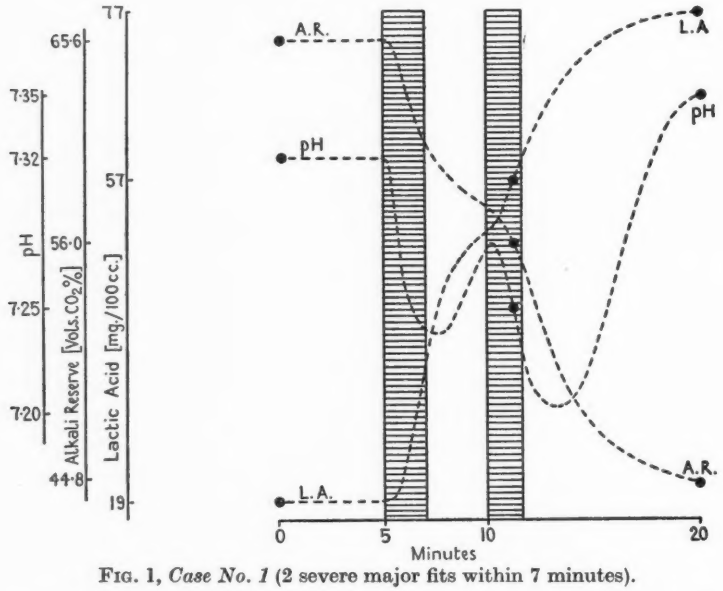

FIG. 1, *Case No. 1* (2 severe major fits within 7 minutes).

2. *Individual cases. Case No. 1* (Fig. 1). During the morning of the day of investigation the patient had a series of attacks consisting of major fits at 7 a.m. and 9.30 a.m., and minor fits at 10.30 a.m. and 11.10 a.m. She was still stuporose but of good colour and breathing quietly when the first blood-sample was taken at 11.50 a.m. At 11.55 a.m. the patient became rigid and cyanosed, and developed generalized clonic contractions, lasting two minutes, before relaxing into a stuporose state. At 12 noon venepuncture was about to be made when the patient had another major fit. A puncture was performed during the seizure, and at 12.10 p.m. a third blood-sample was taken, the subject at this time being restless and overactive. She was still somewhat stuporose half-an-hour later, full recovery taking place in about two hours. No further attack took place for six days.

Case No. 12 (Fig. 2). This patient had a moderate major fit at 9.15 a.m. on the day of investigation. A blood-sample was taken at 11·45 a.m. At 12 noon the patient was pale and said that he was about to have a seizure.

A vene-puncture was performed, the patient being quiet and co-operative. At 12.15 p.m. he had a short aura, a sensation of coldness in the right leg, and 'buzzing' in the head. His eyes rotated upwards, the head extended, and he fell, with generalized muscular twitchings lasting about twenty seconds. A blood-sample was taken. The patient recovered quickly and spoke at once. Further vene-punctures were made at 12.20 p.m. and 12.45 p.m.

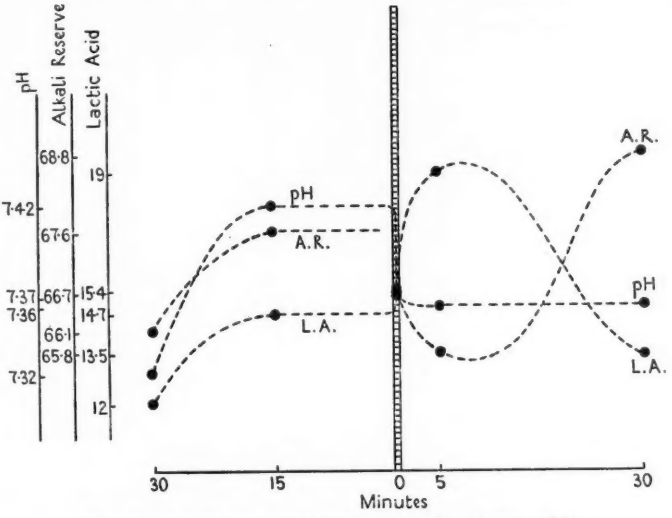

FIG. 2, *Case No. 12* (moderate major fit [20 seconds]).

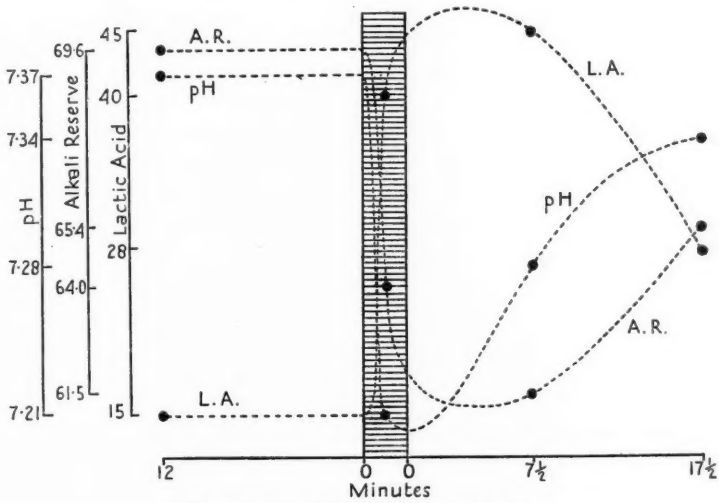

FIG. 3, *Case No. 17* (severe major fit).

Case No. 17 (Fig. 3). The seizure observed was the only one occurring on the day of investigation. A blood-sample was taken at 12.40 p.m. At 12.52 p.m. the patient had a severe major fit, with muscular contractions,

lasting over two minutes. A vene-puncture was made during the fit. Recovery of consciousness took several minutes, the patient then becoming confused and over-active. Further blood-samples were taken at 1.2 p.m. and 1.12 p.m., by which time the patient was quiet.

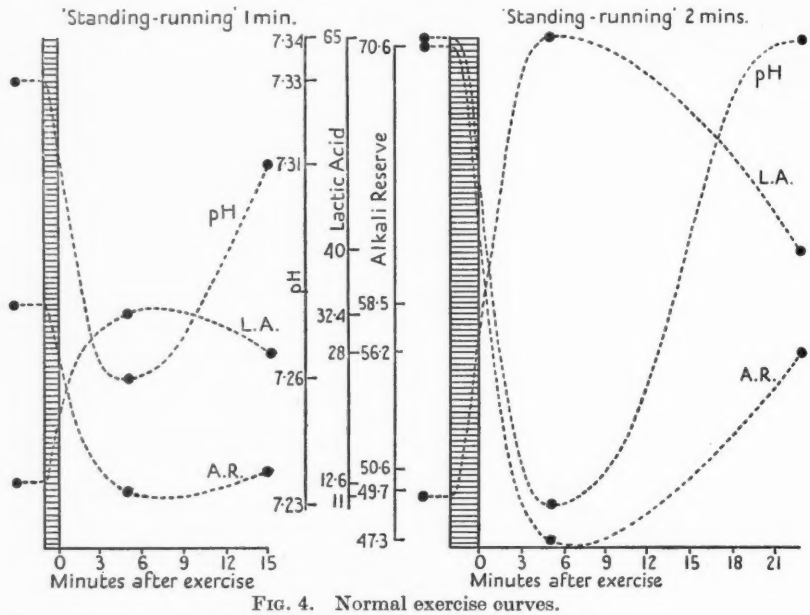

FIG. 4. Normal exercise curves.

It is clear from a consideration of the graphs of Figs. 1–3 that the fall in alkali reserve follows closely the increase in lactic acid, and that subsequent recovery of alkali reserve accompanies the removal of lactic acid. The relation between these is further demonstrated by comparison with Fig. 4, in which 'exercise curves' given by normal individuals exhibit the same features. It is evident that change in alkali reserve caused by the epileptic crisis is accounted for very largely by changes in the concentration of lactic acid in the blood.

The amount of lactic acid accumulating in the blood, as a result of muscular contractions, is related to the efficiency of the recovery process, in which energy derived from the oxidation of a part of the acid is used in the resynthesis to glycogen of the remainder. The first stage of the epileptic fit produces anoxaemia, and this impairs the efficiency of the bodily mechanisms (chiefly liver and muscles) for dealing with the removal of lactic acid. Moreover, many of the muscles involved in the production of lactic acid during the convulsion are not accustomed to dealing *in situ* with large quantities of this substance, and it has been well established by Bock and co-workers (3) and Owles (16) that training is of considerable importance in preventing the leakage of lactic acid into the blood after muscular contractions. There is, therefore, good reason to expect the presence of large

quantities of lactic acid in the blood as a result of severe seizures, and comparison of Figs. 1 and 4 shows that the blood lactic acid was higher after two consecutive fits than after the severe exercise of standing running for two minutes to the point of exhaustion.

The depression of pH during the fit is due firstly to the retention of CO_2 during the tonic stage, and secondly to accumulation of lactic acid during the clonic stage. These have additive effects in increasing the amount of free CO_2 in the blood, and in the case of a severe fit may lead to over-stimulation of the respiratory centre. This is shown in Fig. 1 by an increase in pH a few minutes after the fit to a level higher than the pre-paroxysmal one, in spite of the continued accumulation of lactic acid in the blood. In the case of normal individuals, on the other hand, recovery to the normal pH after exercise appears to be a more gradual process.

It is concluded that changes in the blood constituents discussed in this paper throw no real light on the causation of epileptic seizures.

Summary

1. The acid-base equilibrium of the blood in epilepsy has been studied, measurements being made of pH, alkali reserve, and lactic acid.

2. The results suggest that in the interval period between fits:

(*a*) Variations in alkali reserve and lactic acid are usually within normal limits, but those of pH extend to a range slightly above normal.

(*b*) The average lactic acid concentration is normal. The average alkali reserve and pH values tend to be slightly above normal.

3. The averages of results obtained for alkali reserve and pH during the two-hour period preceding the fit, show no significant difference from those of the interval period.

4. Results obtained from blood-samples of individual patients before, during, and after seizures are illustrated by graphs and lead to the following conclusions:

(*a*) There is a fall in alkali reserve during, and for varying periods after, the fit, this fall being accounted for by the accumulation of lactic acid in the blood. Decrease in lactic acid during recovery is accompanied by increase in alkali reserve.

(*b*) The blood pH falls during the fit, due firstly to apnoea during the tonic stage, and secondly to production of lactic acid during the clonic stage. Recovery to the normal pH is more rapid than is the case with normal individuals after exercise.

The authors desire to express their thanks to Dr. F. L. Golla, Director of the Central Pathological Laboratory, for his interest and encouragement, and to Dr. J. Brander, Medical Superintendent of Colney Hatch Mental Hospital, for his kindness in allowing us to investigate the cases reported in this paper. Thanks are also due to Dr. A. A. W. Petrie, Medical Superin-

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The work described in this paper was carried out during the tenure by one of us (R. H. H.) of the Maudsley Research Fellowship.

Appendix

Case Notes

Case No. 1 (Idiopathic Epilepsy). *W.F.* Girl, aged 22, admitted 18.1.1930. *Family history.* Mother alcoholic. Patient an only child. There is no known history of epilepsy, mental defect, or insanity.

Previous history. Birth, infancy, and childhood apparently normal. At age of 14 patient began to have epileptic fits, which gradually increased in frequency. Menstruation began normally at the age of 14, but stopped, following a fright, at 17. Increase in the number and severity of the attacks, with periodic maniacal outbursts, led to certification two years later. Attacks, mostly major, now average thirty per month. Gradual development of typical epileptic habitus: dull, stupid, and obstinate.

Physical. No abnormality of skull. Optic fundi, normal. No cranial nerve lesion; no muscular weakness or spasticity; deep and superficial reflexes normal; no sensory impairment. No evidence of disease of heart, lungs, or abdominal organs. W.R. blood: negative. Urine contains no abnormal substances. B.P. 98/70.

Case No. 12 (Idiopathic Epilepsy). *R.W.* Porter, aged 23, admitted 22.8.1930. *Previous history.* Labour was normal and no instruments were used. He attended school till the age of 12, when he began to suffer from fits, with generalized muscular spasms and loss of consciousness, followed by a short period of stupor. There is no known history of head injury and no family history of epilepsy or insanity. A year before admission a seizure occurred when the patient was in a swimming bath, and this was followed by pneumonia. He was taken to a general hospital where he had 100 fits in a few days, followed by profound confusion and restlessness. Fits now average forty per month.

Physical. A short, well-developed man, with slight exophthalmos. Repeated examination of the nervous system has revealed no evidence of any organic disorder. No evidence of disease has been found in the lungs, heart, or abdomen. W.R. of blood, negative. Urine contains no abnormal constituents. There is no skull abnormality. B.P. 110/75.

Case No. 17 (Idiopathic Epilepsy). *S.B.* Aged 28, admitted 11.10.1919. *Previous History.* 'Convulsions' were noticed at the age of eighteen months, the patient's mother attributing these to a fall on the head occurring at this time. At the age of 10 the patient was sent to an epileptic colony. There was a gradual increase in the frequency of attacks of the typical 'grand mal' type. He became very dull and retarded, and was removed to a mental hospital. Fits now average fifteen per month.

Physical. There is no evidence of organic disease in the nervous system or elsewhere. W.R. negative.

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CRITICAL REVIEW

ACHLORHYDRIA

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The acidity of normal gastric juice was demonstrated probably in the first instance by Réaumur (1752) and later by Spallanzani (1780), but it was not until 1832 that Prout and then Tiedemann and Gmelin showed that this was due to hydrochloric acid. The use of the stomach tube for withdrawing samples was not employed until much later by von Leube (1879), the method of the one-hour test meal being employed by Ewald, Boas, Hayem, and others.

In 1893 Gross suggested a soft Nélaton catheter as an alternative to the previously employed large-bore tube, but its value does not appear to have been appreciated until Ehrenreich, Einhorn, Rehfuss, and Ryle (1920) demonstrated the greater value of the fractional method of gastric analysis over the older one-hour sample Ewald breakfast, with which many fallacies are associated.

Using this method of investigating the various phases of gastric function, an enormous literature has developed, and it has been shown that the separate elements of the gastric secretion may be absent or diminished in a large variety of diseases. The difficulty of detecting satisfactorily and quantitatively those constituents other than the hydrochloric acid and chlorides has led to the acquisition of much knowledge regarding the latter, but little about other co-existing substances such as pepsin, mucus, and the haemopoietic factor ('haemopoietin'—Wilkinson and Klein, 1932) amongst others. An absolute deficiency of hydrochloric acid is referred to as achlorhydria, while achylia gastrica is considered to indicate the complete absence of all gastric secretions, although this is not strictly correct, since mucus and an aqueous fluid containing some chloride at least are always secreted to a variable amount, even in the most severe cases. These terms have been used synonymously by some writers, thus causing much unnecessary confusion, and it is desirable to appreciate and maintain these differences.

In recent years it has been realized that many cases of apparent achylia or achlorhydria were not strictly so, since they could be induced to secrete free hydrochloric acid under certain circumstances—mainly after the use of gastric stimulants such as histamine.

Histamine. The considerable physiological interest (Dale) associated with the amine, histamine, which had been synthesized by Windaus and Vogt in 1907, led to the investigation of its intense stimulating effects upon the gastric secretory glands in health and disease. (Carnot, Koskowski, and Libert; Lim, Matheson, and Schlapp; Matheson and Ammon; Dobson; Gompertz and Vorhaus; Stüber and Nathansohn; Katsch and Kalk; Faber and Holst; Polland and Bloomfield; Polland and Roberts; Vandorfy; Wright, 1928; Gompertz and Cohen; Johansen; Wilkinson, 1932; Hartfall, 1933.)

By its use it has been shown that many cases previously considered to have had achlorhydria or achylia were able to secrete free acid under its influence. Doses of 0·25 to 1·0 mg. have been used, but the smaller ones appear to be quite as effective as the larger ones. It should be noted, however, in passing, that Streicher does not consider its use justified owing to its toxic effects. Hurst (1923) prefers gastric lavage, followed by the ordinary gruel test meal, while other observers (Eggleston) do not believe that its use is necessary for practical purposes. In general, the consensus of opinion is that histamine furnishes an excellent gastric stimulant whereby it can be demonstrated that true achylia gastrica is a comparatively rare occurrence and most commonly associated with pernicious anaemia (Faber and Holst; Katsch and Kalk; Johansen; Wilkinson, 1932; Hartfall, 1933); this may be of considerable diagnostic importance.

It has been suggested more recently (Babkin; Vineberg; Gilman and Cowgill) that in dogs with Pawlow or Heidenhain pouches histamine stimulates the secretion of hydrochloric acid exclusively, but this has not been the experience of Blakely and Wilkinson in human subjects where the secretion of both acid and enzymes appear to be stimulated. This will be discussed in another place. The question is of considerable significance in view of the increasing importance of achlorhydria gastrica and the experimental work that has been carried on recently upon the haemopoietic factor present in gastric juice of normal and abnormal individuals (Castle; Wilkinson; Wilkinson and Klein 1932, 1933; Hartfall and Witts 1933).

Achlorhydria in Apparently Normal Individuals

The occurrence of achlorhydria in apparently healthy individuals has received comparatively little attention in the medical literature, probably on account of their unwillingness to be the subjects of such investigations.

Since the earlier observations were based upon single gastric samples in each case little weight can be attached to them. In a few other more recent series of observations, however, using the fractional methods of gastric analysis, various figures have been indicated suggesting an increasing occurrence of achlorhydria with increase in age. It should be noted that comparatively little has been done, except in a few cases with regard to the secretion of chlorides and pepsin.

Bennett and Ryle examined a series of 100 apparently healthy university students, finding only 4 with achlorhydria, and Dahl-Iverson saw 11 per cent. with achylia in 128 normal persons. Baird, Campbell, and Hern observed 1 case out of 57 students, while Apperley and Semens noted 8 in a group of 90 similar subjects; there was apparently a probable familial tendency in 2 of the latter, since one parent in each case had suffered from pernicious anaemia and rheumatoid arthritis respectively—conditions associated with achlorhydria (Wilkinson and Oliver, *vide infra*). Rehfuss (1929) is sceptical about the occurrence of normal achlorhydria, and believes that 'a careful study will reveal some abnormality in their make-up', while Cheney (1926) says that it seems reasonable to conclude that achlorhydria never occurs in the normal individual, and that it may be the forerunner of several vital ailments has been definitely proved. Apperley and Semmens found, also, that achlorhydria was much more common amongst the students of subnormal mentality, but a more striking feature was the finding of achlorhydria in 30 per cent. of healthy female students (Apperley).

Bloomfield and Keefer believe that anacidity is a common occurrence, often without clinical significance.

In a review of 3,381 fractional gastric analyses carried out on patients with apparently normal gastro-intestinal tracts, Vanzant, Alvarez, Eusterman, Dunn, and Berkson found that achlorhydria increased with age, rising from 4 per cent. at the age of 20 years to 26 per cent. at 60 years of age, the average for the whole series being 12·1 per cent. The females were apparently more liable to show achlorhydria than males at all ages.

There was a decrease in incidence after 70 years of age. Vanzant also noted the highest incidence of 30 per cent. in the sixth decade. Seidélin found impaired acidity (achlorhydria or hypo-acidity) in 40 per cent. of working-class patients over the age of 50 years and 67 per cent. over 67 years of age, while Faber (1927) observed a similar anacidity occurring in 50 per cent. of individuals over 50 years of age. Dedichen, apparently using the Ewald meal, found 66 per cent. of 99 healthy old people, between the ages of 67 and 92 years, and Liefschütz 37 per cent. in patients over 50 years had achlorhydria or achylia, while Meulengracht noted an even greater incidence (74 per cent.) in old people over 60 years, but the Ewald meal was used in some of these cases. Similar observations were made by Keefer and Bloomfield (1926) and by Gilford.

On the other hand, Rafsky and Kruger only found 1 case with achlorhydria in 75 old people of 70 to 91 years of age, but Davies and James, examining 100 people between 60 and 95 years of age, found 32 per cent. with apparent achlorhydria, but only half of these failed to secrete free hydrochloric acid after the use of histamine.

Bockus, Bank, and Willard observed a gradually increasing incidence of achlorhydria with advancing years from 1·3 per cent. in the third decade to 15·4 per cent. in the seventh decade, the females showing greater numbers than males. In 210 cases of achlorhydria there were 110 females to 100

males. Hurst (1932) and Hartfall (1933), excluding cases of carcinoma of the stomach, pernicious anaemia, and artificial achlorhydria following gastro-intestinal operation, found an average of 10·3 per cent. achlorhydria in 2,356 patients, there being only 4 per cent. between 10–19 years, slowly rising to 16· 6per cent. at 70–79 years. Considering the sexes separately they found that achlorhydria was more common in females (13·2 per cent.) than males (7·5 per cent). The latter remained fairly constant at about 10 per cent., but the former showed increasing values with each decade.

Achlorhydria in Children

Martius noticed that a large number of young children and infants had reduced gastric acidities, and considered this as evidence for a congenital occurrence. Weinberg found achylia in nine children without anaemia, one parent of each having had pernicious anaemia, and he actually reported three with achylia out of four children in one family. Jacobsen, however, found that many children with gastric symptoms did not show any prominent tendency to achlorhydria, although it did occur amongst those with acute intestinal affections; Bloch (1923) found a lowered secretion in more than half his cases with intestinal lesions, and 25 per cent. of the infants had a complete achylia that persisted for periods of several weeks up to eleven months. Similar observations were made by Hertz, Chievitz, Andersen, and Klementsohn, who examined series of healthy children and failed to find any evidence of a congenital or constitutional origin for achlorhydria. From an examination of normal infants, Davidsohn (1921), Marriott and Davidson (1923), Babbott, Johnston, Haskins, and Shohl (1923), and Davison (1925), amongst others, found that gastric samples withdrawn at the height of digestion usually showed values of pH 3·0–pH 5·0, few cases falling below pH 3·0, but there was an increased acid production with increased age. Since the healthy adult's gastric juice is approximately pH 1·2–1·4, and free hydrochloric acid is not detected until the pH is near 3·0, it will be seen to be of the order of a 100-fold to 1,000-fold more acidic than was found in these normal infants. It is probable that the gastric juice of such infants is not fully developed until later. Wright, using the Ewald meal, found achlorhydria in only 1·6 per cent. of 250 normal children between the ages of 6 and 15 years, Katsch only saw a few cases, and Bunce quotes a figure of 1·5 per cent. Copeman and Hill, on the other hand, noted 10·6 per cent. in a group of sixty-six between 12 and 15 years, and Bray (1930) found less than 10 per cent. among normal children. Since extensive statistics are lacking, it would appear difficult to assess accurately the frequency of achlorhydria in early childhood and infancy. Using the alcohol meal, Neale found no instance in which he was able to promote the flow of acid in a large series of normal children.

Achlorhydria in Disease

The occurrence of achlorhydria in general disease other than artificially produced gastric anacidity has been much more fully investigated, and combining both sexes it appears to be of the order of 10 to 15 per cent. from the observations of Andresen (10 per cent., 4,000 cases); Eggleston (10 per cent., 2,700 cases); Hartfall (10·3 per cent., 2,356 cases); Vanderhoof (10·5 per cent., 4,281 cases); Larimore (12·2 per cent.); Hurst (1928) (15 per cent., 712 cases); Kohiyar (15 per cent., 1,030 cases); Connor (15·2 per cent., 5,000 cases). On the other hand, Friedenwald and Morrison only saw 0·7 per cent. in 1,592 cases.

Apperley (18 per cent., 200 cases) and Nye and Sippe (21 per cent, 350 cases) obtained somewhat higher figures, and it is suggested that the greater incidence of achlorhydria observed by these workers may be due to the tropical climate which apparently tends to diminish the gastric acidity (Apperley; Borchardt) and to produce alkalosis (Sundstroem; Apperley and Semmens). From their own figures Nye and Sippe found achlorhydria in 17·8 per cent. of their cases during the cooler months of the year, but 26·5 per cent. in the hot months.

Nyman, however, concludes that there is an increased incidence of achylia in the winter months. There is further evidence that achlorhydria without the association of pernicious anaemia or subacute combined degeneration of the spinal cord may be familial and quite unassociated with any signs or symptoms, although these cases are usually detected by a systematic examination of the relatives of cases complaining of gastro-intestinal disturbances such as flatulent dyspepsia, chronic diarrhoea, or sore tongue (*vide infra*). Such cases have been described by Albu (1913), Hurst (1932), Jung (1902), Martinez (1927), Schneider and Carey (1928), Udaondo (1923), Wilkinson and Brockbank (1930), and Wilkinson and Oliver (1931). Golob has recently reported a familial achylia in two brothers, a sister, and a half brother; the two latter died of gastric cancer; in addition two other sisters had diabetes mellitus—a condition in which achlorhydria is often found.

Aetiology

The main theories of the aetiology of achlorhydria may be conveniently considered under three headings: (*a*) Those attributing it to a gastritis of exogenous origin; (*b*) those regarding it as a constitutional abnormality; and (*c*) those attributing it to a neurogenic origin.

(*a*) Faber believes that achlorhydria is almost always secondary to a chronic gastritis, usually with an accompanying round-celled infiltration, and occurs particularly after infectious disease. He regards it as a disease of the glandular parenchyma of an inflammatory nature, and says that in children this structure is very labile, while the damage ensuing from

infectious disease may persist for a lifetime; he does not subscribe to the view that it is hereditary or familial in character. Bloch (1923), Faber, Faber, and Lange, Hurst, Meulengracht, and Rehfuss have also noted the frequent occurrence of achlorhydria or achylia after pneumonia, influenza, tonsillitis, enteritis, and other acute infectious toxic or irritant causes. Certain infectious diseases and fevers (Meyer, Cohen, and Carlson) have been investigated by many workers, mainly by means of the Ewald meal: the absence of free hydrochloric acid in the gastric juice after typhoid was observed by Van den Velden, Thaysen and Wegge, Rehfuss, and Meulengracht. Frankl and Plaschkes report 25 per cent. cases of anacidity after typhus, and after paratyphoid 50 per cent. anacidity, while Schroeder, in an investigation of an epidemic of dysentery in Strasburg, found that 18 out of 37 cases had achylia. Tørning found achylia gastrica in 6 per cent. of 150 patients with pulmonary tuberculosis, while Permin also found an increasing percentage of achlorhydria as the disease progressed to as much as 75 per cent. in advanced tuberculosis. Rave has also considered the question more recently. It is probable that the association of a gastric secretory dysfunction with eclampsia (Petersen), emesis and hyperemesis gravidarum (Arzt, 1926, 1930; Mason, 1931; Anderson, 1932) may be due to similar causes, but the depression appears to be only temporary in most of these cases.

Guido found that 26 per cent. of his malarial patients had an achlorhydria that frequently persisted throughout life.

(*b*) The theory of the constitutional origin of achlorhydria is supported by its tendency to occur in many members of a family. Martius, Hurst, Udaondo, Martinez, Eggleston, and Wilkinson have all quoted instances of this, and in some cases it has been shown to occur through several generations.

Udaondo states that the achylia is often attended by other constitutional peculiarities such as dental anomalies, bradycardia, neurosis, oxaluria, phosphaturia, and albuminuria.

Hurst (1932) and Hartfall (1932) found no increasing anacidity with age in males, as would be expected if it was due to chronic gastritis, although the tendency did increase with age in females; in men achlorhydria was constant for each decade.

Bockus, Bank and Willard say that they have not demonstrated that gastritis is the usual cause of achylia, while Wilkinson and Brockbank (1930) and Connor have shown that achlorhydria is more frequent in relatives of cases suffering from pernicious anaemia. They think that there is an inherited tendency to develop achlorhydria later in life, and in investigating cases of gastritis found a true achylia in only 12 per cent. of the cases.

Hurst (1923) says that the pathological changes in the stomach in achylia are so slight and patchy that there can be no question of the achylia being due to actual destruction of the secretory cells and says: 'I believe it is much more common for gastritis to be secondary to achylia than for achylia to result from gastritis', concluding that 'it must be due to an inborn

deficiency in the functional capacity of the glands, which appear to be structurally normal'.

Bauer believed that a persistence of the infantile glandular state might mean the under-development of the acid secretory elements, but the profound influence of slight malaise, pyrexia, or disease on the gastric secretion of infants makes this difficult to interpret. Martius considers that chronic achylia gastrica is due to a congenital abnormality and is not secondary to a gastric atrophy.

(*c*) The neurogenic origin of achlorhydria is supported by the presence of functional nervous symptoms in a large proportion of the cases, a fact which is emphasized by all investigators. Schmidt considers achylia to be due to anomalies of innervation, and Stiller regards it as an element of the asthenic type of individual. Albu believes that there is a congenital functional debility of the gastric mucosa, but Disqué suggests a neurogenic factor leading to its functional depression. Both Schmidt (1911) and Cheney (1926) draw attention to the frequency of achylia in constitutional ptosis and Glénard's disease, in both of which neurasthenia is a prominent symptom. According to the latter, achlorhydria never occurs in the normal individual. The observations of Bennett and Venables that gastric secretion can be depressed under hypnosis emphasizes the part played by the nervous system in the control of gastric secretion. The increased incidence of achlorhydria in Graves' disease with the duration of the illness may also support thet heory of nervous control. Taking a wider view, Rosnowski and Marczewski regard achylia as a disease not only of the stomach but of the intestine, pancreas, liver, and blood in addition. Bennett (1930) has described an 'asthenic achylia' in which the achlorhydria was apparently due to a general visceral asthenia associated with a peripheral neuritis with foot-drop and anaesthesia.

The Symptoms of Achlorhydria

The symptoms and diseases associated with achlorhydria are so numerous that a classification is a matter of some difficulty. They may be divided into—

I. Those apparently entirely functional and referred to (*a*) the gastro-intestinal tract, and (*b*) other organs.

II. Symptoms associated with organic disease.

I. *Functional symptoms.* (*a*) Of the functional symptoms associated with the gastro-intestinal tract probably the most prominent is flatulence, which may have been present intermittently for a great many years and led to a suspicion of gall-bladder disease. Vomiting is uncommon, but in some cases nausea is complained of, and there may even be 'acidity' and heart-burn (Zweig). Bowel disturbances are also common, constipation or diarrhoea, or both, occurring alternately. According to Hunter (1923) the diarrhoea is usually in the early morning, before breakfast, or just after meals, and the stools are loose and watery. Mucus is sometimes present, but apart

from ulcerative colitis there is no blood. Undigested meat fibres may be seen in the stools owing to the rapid passage of the intestinal contents (Ryle, 1924). The diarrhoea may be accompanied by discomfort, but real pain is exceptional. A secondary catarrh of the gut may lead to such extreme diarrhoea that alimentation is affected and the patient loses weight to such an extent as to lead to a diagnosis of carcinoma (Zweig). However, Eggleston found constipation to be more frequent than diarrhoea and said it was present in more than 75 per cent. of his cases. Occasionally epigastric pain is prominent and there may be fullness and oppression after food, sometimes a tearing pain like a hyperacidic complaint.

Eggleston has also drawn attention to the similarity of the symptoms to duodenal ulcer. Eusterman (1931) considers that with the exception of those cases simulating ulcer, there is no proof that the symptoms referable to the stomach are due to the achlorhydria by itself; in the absence of gastritis he believes that the majority of the symptoms are of neurogenic nature. We have seen three cases in which pain was the outstanding feature, and in one it was so severe that a laparotomy had been performed for a suspected cancer of the stomach. Usually the pain is more continuous than that met with in ulcer and is suggestive of a 'neuralgia' of the stomach.

Moore has recorded the presence of pylorospasm in some of these cases, and increased motility of the stomach with rapid emptying is the rule. The appetite is usually poor in contradistinction to ulcer cases in which the patient is afraid to eat.

Another common complaint is of some disturbance of sensation in the tongue. This may vary from an intermittent sensation of discomfort without any physical signs whatever, to soreness with a marked smoothness of the anterior two-thirds with atrophy of the papillae, or to actual ulceration. This ulceration is often intermittent and comparatively trivial, but in one case which came under our notice it had persisted for over ten years, had made life almost unbearable, and three times had been associated with an attack of dermatitis herpetiformis.

Although these tongue symptoms are common in anacidity and may be a useful clue in arriving at a diagnosis, it must not be assumed that a sore tongue necessarily indicates diminished acidity, for in a number of cases there is an excess of acid which we have often demonstrated; Sellei also draws attention to this.

Keefer, Yang, and Huang, studying anaemia and chronic dysentery, record this tongue condition in many of their cases and find it occurs with or without anaemia or achylia; as it clears up when the patient is put on a proper diet they regard it as evidence of a deficiency disease.

The physical signs are usually few or absent. The patient is often of the asthenic habitus, as mentioned above, or suffers from Glénard's disease, and there may be vague abdominal tenderness, chiefly over the descending colon. Succussion splashes and gurgling over the bowel are also common.

Occasionally the liver is slightly enlarged and tender.

(*b*) The functional symptoms associated with other organs are related chiefly to the nervous system. The patient frequently is of a neurotic type, tires easily, and complains of a lack of vitality. Depression, sleeplessness, and migraine are common. Sometimes wasting may be a prominent symptom, and this together with the chronic fatigue may lead to a diagnosis of phthisis. In one case under our care the patient was so wasted and easily fatigued that he had been unable to work for three years, but after a few weeks of treatment with hydrochloric acid felt fit to return to his old occupation and has continued at it ever since.

Eggleston also has drawn attention to chronic fatigue as a prominent symptom in achylia. There may be a great intolerance to cold and a very dry skin, as we have frequently noted.

Davies and James found that their patients were often unusually pale although the blood counts were practically normal.

II. *Achlorhydria and organic disease.* Achlorhydria may be associated with organic lesions arising in the diseases of (*a*) the gastro-intestinal tract, (*b*) the blood, (*c*) the nervous system, (*d*) the endocrine system, (*e*) the joints, (*f*) allergic origin.

(*a*) *Gastro-intestinal tract.* The presence of anacidity in a large number of organic lesions of the gastro-intestinal tract is now well recognized.

In association with *diseases of the gall-bladder* (cholecystitis and cholelithiasis) Hartfall (1932) found achlorhydria in 12·3 per cent. of his cases, Eggleston 13 per cent. in 100 patients, and Eusterman 15·3 per cent. in 2,290 cases, while Hartman and Sagar observed 89 patients with chronic gall-bladder disease in a series of 492 with anacidity. Moynihan reported 22 per cent., Cheney (1926) 25 per cent., and Bonar 47 per cent. of their cases showing anacidity with cholecystitis. Gatewood, using the Ewald meal, found that 30 per cent. of his cases with diseases of the gall-bladder had achlorhydria. The gastric condition was apparently unaffected by age, jaundice, site of gall-stone, or operation. Similar investigations were made, also using the Ewald meal, by Hohlweg (1910, 1912), Wohl (1917), Rydgaard (1921), Rohde (1921), and Dangschat (1923). Hartman and Rivers concluded that there was no alteration in the original gastric acidity after cholecystectomy, but Dowling found that 64·5 per cent. of his gall-bladder patients had achlorhydria or hypochlorhydria. Dahl-Iverson considers that the lowered secretion of chyle in patients with gall-stones and the dyspepsia between the gall-stone attacks can be explained by the hypochlorhydria or achylia. Jarno records a high blood cholesterol in anacidity, and considers it an important feature of these cases, and Hines describes eight cases of achlorhydria giving abnormal cholecystograms. According to Cheney (1926) the most probable explanation of the association of achlorhydria with gall-bladder disease is that chronic gastritis and cholecystitis occur together, and he says that if achlorhydria exists before the removal of the gall-bladder it persists afterwards. It should be noted, however, that the intravenous

administration of bile to dogs produced inhibition of gastric motility and secretion (Still and Carlson, 1929).

Other diseases of the liver may be associated. Hartman and Sagar found three cases of cirrhosis of the liver in 492 cases of achlorhydria, and Hartfall (1932) records four cases in his series. Rosnowski and Marczewski think this is due to a loss of bactericidal power of the duodenum leading to an excessive and abnormal bacterial growth in the whole intestine and the toxins invade the portal system.

One of us (Susman and Oliver) has recorded a case of subacute yellow atrophy in which a complete absence of hydrochloric acid had been demonstrated many months before the fatal termination.

Chronic gastritis. Whether achylia is invariably a sequel of a chronic gastritis is still a matter of dispute. Certainly it appears to be a primary condition in a large number of cases. Faber (1927) maintains that this is invariably the case, and recognized two factors, a haematogenous one due to an acute infection, which is the common cause in childhood, and a direct irritation due to such conditions as unsuitable food or alcohol. He holds that lack of acid is the first indication of a developing gastritis. Hayem and Lyon found an alteration in the gastric mucosa going on to atrophy in cases where the hydrochloric acid secretion was absent, and Apperley and Norris consider anacidity to be due to a chronic gastritis, regarding it as a precursor of cancer of the stomach. Kauffmann stresses the importance of chronic tonsillitis, apical teeth infection, and pharyngitis in producing a chronic gastritis, and he observed fatty degeneration of the gastric mucous membrane in dogs in which he had produced sterile abscesses or inflammation of the skin, which strongly supports the possibility of a haematogenous source in addition. Thomsen was able to produce acute gastritis in dogs followed by gastric anacidity, by the administration of diphtheria toxin intravenously, or by alcohol by mouth. Vogelius found that cases of alcoholic gastritis with free acid in the gastric secretion showed achylia a few years later; over 50 per cent. of these cases of alcoholism showed evidence of gastritis. Konjetzny believes that gastritis is the cause of ulcer and of carcinoma, and found gastritis in every case of gastric ulcer examined, and duodenitis and gastritis in every case of duodenal ulcer.

Hurst (1932) says that achylia gastrica may be due to a familial condition or to atrophic gastritis, while achlorhydria is due to a chronic non-atrophic gastritis, in which acid may return after treatment. He advocates the performance of a second test meal after a preliminary lavage as a diagnostic test, and the presence of acid in this would serve to differentiate the two. He refers to cases of pernicious anaemia in which the onset of symptoms dated from an attack of acute gastritis.

Arafa suggests that hypertrophic and atrophic gastritis are merely stages of the same condition, and draws attention to the fact that mucus is only exceptionally present in these cases. Cheney (1926), however, regards mucus as the characteristic feature of the disease.

On the other hand, Hartfall thinks that achlorhydria cannot be explained as an expression of a developing gastritis, but rather as a senile atrophy of the mucosa.

Dahl suggests that achylia is due to an effect of a chronic inflammation of the antrum, in which the epithelium is destroyed, so that its function, which is to facilitate the secretion of the fundus, is interfered with, and there is therefore no gastric juice even if the latter be normal.

Porges recognizes two forms of gastritis, a pyloric and a fundic; in the former there is a high and in the latter a low acidity. In this connexion Morley and Roberts, investigating the acid secretion after partial gastrectomy, found that the achlorhydria was due to absence of secretion and not to neutralization of the acid. They regarded their results as indicating a disorganization of the reflex or hormonal relations between the different parts of the stomach following the operation, and not to actual diminution of the secretory surface.

The relationship of achlorhydria to cancer of the stomach is still a matter of dispute, and many observers thought that free hydrochloric acid in the stomach contra-indicated a diagnosis of malignancy. However, it has been frequently shown in recent years that cancer of the stomach may be associated with achlorhydria in from 50 per cent. (Hartman), 65 per cent. (Hurst, 1929), to 90 per cent. (Friedenwald, 1914) of cases.

Konjetzny was the first to draw attention to chronic gastritis as a possible aetiological factor in cancer of the stomach. Hurst (1929) maintains that achlorhydria is the result of chronic gastritis, which precedes the onset of carcinoma and is the commonest predisposing condition, and he divides gastric cancer into two groups, a primary following chronic gastritis, and a secondary following on a chronic simple ulceration. Seventeen out of 19 of his cases of cancer of the stomach with less than six months' history had achlorhydria, and these he regards as primary, but only 1 in 11 cases which followed simple ulceration. When free acid is present the cancer is secondary to ulcer, when there is achlorhydria it is secondary to chronic gastritis. He quotes Porges as saying that achlorhydria was found to be present many years before the appearance of symptoms of carcinoma. Orator found achlorhydria in 7 out of 8 cases where the cancer appeared to be primary. The latter found a well-marked atrophic gastritis present throughout the stomach in these 'primary' cancer cases. Hartman and Sagar observed 93 cases of gastric carcinoma in their series of 492 cases with achlorhydria, but, on the other hand, only 17 cases in their series of 420 patients with hypo-acidity. Apperley and Norris also support Hurst's contention that achlorhydria is a result of chronic gastritis and precedes the appearance of cancer. Arafa suggests a parallel with chronic glossitis and chronic mastitis in producing malignant degeneration.

On the other hand, nearly all investigators, ourselves among them, have found that achlorhydria is much more common in women, while cancer of the stomach is much commoner in men.

In men, too, according to Hartfall (1932) anacidity does not increase with age, as would be expected if it predisposed to cancer. The combination of pernicious anaemia (with absolute achylia gastrica) and cancer is relatively very common, and one of us has reported two cases of gastric carcinoma and six others with malignancy in other organs, while only twenty-five other authentic cases of such a combination have been collected from the medical literature (Wilkinson, 1933). Of all these only three (Strandell, Plummer, Wilkinson) have been observed to develop the malignant condition following previously diagnosed pernicious anaemia with achylia—the onset occurring during remission following adequate anti-anaemic treatment. On the other hand, Wilkinson (1933) has recently discussed the incidence of pernicious anaemia following gastric resection for carcinomata in eleven cases, where presumably achlorhydria was produced. In the light of recent work, however, the vital deficiency was most probably not the hydrochloric acid but 'haematopoietin' (Wilkinson and Klein), although an inefficient intestinal absorption of its reaction product would produce a similar effect.

In organic disease of the stomach, apart from chronic gastritis, achlorhydria is by no means uncommon.

Hartman and Sagar report 13 cases of gastric ulcer in their 492 cases of anacidity, while Bell, investigating 27 cases of proved gastric ulcer, found a complete achlorhydria in 4 and a marked hypo-acidity in 3. He says that clinically they were indistinguishable from the cases with a normal amount of acid. Moynihan found that 13·5 per cent. of his gastric ulcer cases had achlorhydria and Hunter (1923) 3 out of 20 cases.

Hurst (1929) attributes this achlorhydria in chronic ulcer cases to the associated chronic gastritis. Bell draws attention to the rarity of achlorhydria in duodenal ulcer, only seeing 1 in 40 cases. Moynihan gives a figure of 5·5 per cent., and 1 case each is reported by Hartfall (1932) and by Hardt. The latter, however, does not state whether the diagnosis was confirmed at operation or *post mortem*, and in Hartfall's case the achlorhydria was due to excessive neutralization, a second meal showing the presence of a small quantity of acid. Crispin mentions 11 cases of duodenal ulcer associated with achlorhydria by the Ewald one-hour test-meal, 3 of them also having gastric ulcers. Although ulcer of the duodenum is rare, Bockus, Bank, and Willard found a duodenitis in 59 per cent. of their cases.

On the other hand, Kohn states that complete achlorhydria excludes gastric and duodenal ulcer, and Bockus, Bank, and Willard (1932) and Horner found no case of duodenal ulcer associated with it in their series of cases.

The Effects of Gastrectomy and Gastro-enterostomy on the Secretion of the Stomach

Total gastrectomy is necessarily followed by achylia, and many of the survivors have developed severe anaemias, cases of pernicious anaemia

developing many years afterwards (Wilkinson, 1933). The effects of partial gastrectomy on stomach acidity have been investigated by several workers, and Klein found that these cases could be divided into three groups. In one anacidity persisted throughout the period of test, in a second there was anacidity for the first one to one and a half hours, and in the third acid was present throughout.

Morley and Roberts found achlorhydria in 12 out of 14 cases after Schoemaker's gastrectomies, and from an estimation of the chlorides concluded that this was due to absence of secretion and not to neutralization of the acid.

On the other hand, Hurst (1932) believes that the achlorhydria is due to rapid neutralization by the duodenal juices.

While total and partial gastrectomies are often followed by a simple achlorhydric anaemia (Berg; Gordon-Taylor; Henschen; Lake; Morley; Strauss; Wilkinson) pernicious anaemia is rare, and only a few cases appear in the literature (Benecke; Borgbjaerg and Lottrup; Breitenbach; Delore; Dennig; Hangarter; Hochrein; Rowlands and Simpson; Scheidel; Wilkinson).

Gastro-enterostomy does not appear to be followed usually by achlorhydria, and Lewisohn and Feldman, investigating 62 cases of this, found complete anacidity in 1 case only, considering it very rare after this operation; Ryle (1924) also noted a similar case. Alvarez says that free and total acidities are reduced from a quarter to a half in four-fifths of the patients. Glanvill and Hurst have recorded one case of pernicious anaemia developing after a gastro-enterostomy, in which the secretion of acid had been proved before the operation, and complete achlorhydria was found three years later. Other cases of pernicious anaemia after this operation have been observed by Conybeare, Horder, Housten, Hurst (1932), Langdon-Brown, Lublin, Wilcox, and Wilkinson (1933). Davidson's case, on the other hand, still had free acid present. Simple achlorhydric anaemia following gastro-enterostomy is less uncommon, but cases have been recorded by Hurst (1930, 1932), Witts (1930), Davies and James (1930), Meulengracht (1932), and Wilkinson (1933).

Of the diseases of the intestine, Bonar found 35 per cent. out of 65 cases of appendicitis had little or no hydrochloric acid in the stomach, but Hartman and Sagar saw only four cases out of their 492 cases of achlorhydria.

Hartfall (1932) noted achlorhydria in 25 of his cases with appendicitis. Kantor and Sagal (1926), Friedenwald, Feldman and Rosenthal (1929) have observed achylia and hypochlorhydria to be common in mucous colitis, but Bockus, Bank, and Wilkinson only saw 4 per cent achylia in 50 cases. Hartman and Sagar have reported a case of ulcerative colitis with achylia in their series. According to Hurst (1924), there is a greater liability for achlorhydric cases to acquire bacillary and amoebic dysentery, and he has advocated the routine administration of hydrochloric acid as a preventive measure. Hartfall (1932) noted five cases of cancer of the bowel. We also

found achlorhydria in a number of cases of malignant disease of the bowel, and care, therefore, must be taken to exclude the possibility of this before diagnosing a case of diarrhoea as one of functional origin.

The cause of the diarrhoea in these cases is still uncertain. Hurst believes that the lack of hydrochloric acid and pepsin leads to undigested food in the intestines and a subsequent irritation, while the lack of the normal disinfecting barrier of hydrochloric acid also leads to an abnormal intestinal infection; Knott found the duodenal contents full of organisms, with a tendency to be of the faecal type in cases of achlorhydria. Hartfall, however, cannot accept this view, as gastric hurry is not necessarily associated with diarrhoea, and he has not been able to demonstrate abnormal intestinal infection in cases of achlorhydria with diarrhoea as compared with those associated with constipation. It is difficult to account, certainly, for the immediate cessation of diarrhoea in some of these cases on the administration of hydrochloric acid; possibly it may be due to an effect on the central nervous system on the analogy of the increased movements of the stomach and intestines seen in hypoglycaemia, which appear to be due to this.

Emery does not think absence of hydrochloric acid is the cause of the diarrhoea, and believes it is really a symptom of the same condition. The occurrence of diarrhoea after gastro-enterostomy (Ryle, 1924; Lehmann) may be a similar phenomenon. Farrell, studying the effect of colitis on gastric digestion, found the gastric secretion depressed in both mild and severe colitis, a mild colitis hastening emptying of the stomach but a severe one retarding it.

Achlorhydria Associated with Diseases of the Blood

The gastric secretion in pernicious anaemia has been fully considered by one of us (Wilkinson, 1932), and it has been shown that pernicious anaemia is almost always associated with achylia gastrica, as has been pointed out by Hurst. The possibility of a close association between the gastric juice and pernicious anaemia was suggested by Flint amongst others.

Undoubtedly Fenwick saw some cases of pernicious anaemia in his description of atrophy of the stomach, but Cahn and von Mehring first drew attention to the lack of free hydrochloric acid in this condition. Martius observed that 2 of his cases with achlorhydria had died of pernicious anaemia, while Faber and Bloch, in 1900, observed a similar association in 33 cases of pernicious anaemia. Since then a large number of writers have made similar observations, using the Ewald one-hour test meal (Ewald; Faber and Bloch, 1900; Hutchison; Martius; Weinberg; Zadek). With the introduction of the fractional method of gastric analysis the profound gastric secretory dysfunction has been still further emphasized (Cabot; Carr; Campbell and Conybeare; Davidson and Gulland; Faber and Gram; Hurst; Levine and Ladd; Panton, Maitland-Jones and Riddoch; Percy; Sheard; Wilkinson; Willson and Evans) and supported by the lack of response following the use of the powerful

gastric stimulant histamine (Hartfall; Johansen; Katsch and Kalk; Wilkinson, &c.). Wilkinson (1932) reported a series of 200 proved cases of pernicious anaemia, and found complete achylia, while of 8 others with free hydrochloric acid present in the gastric juice 2 were cases of 'haemolytic' anaemia of pregnancy, the other 6 being apparently Addisonian anaemias. He collected some 66 other cases from the literature. Since then 2 further cases have been described by Moore and O'Farrell (1933) and Hartfall (1933). The extreme rarity of these cases is so marked that very grave doubts must often be entertained as to the correctness of the diagnosis. In the whole literature, therefore, there appear to be only some 74 (Wilkinson, 1932; Hartfall, 1933; Moore and O'Farrell, 1933) of these cases, many of them having been very inadequately reported, and must be regarded as doubtful.

It is of significance, however, that Seyderhelm and Opitz, Connery and Joliffe, McPeak and Neighbors, and Wilkinson (1932) have reported apparently true cases of pernicious anaemia which have shown the return of free hydrochloric acid at varying periods after the institution of liver treatment, while Hurst (1932) has been successful after regular gastric lavage with this object in view. In the majority of cases of pernicious anaemia the achlorhydria is a permanent condition unaffected by remission or relapses, so far as is possible to determine in the light of our present knowledge.

Various theories have been put forward from time to time in order to explain the almost invariable association of achylia gastrica with pernicious anaemia. Recent work (Castle; Wilkinson; Wilkinson and Klein; Klein and Wilkinson) would suggest that it is of less importance from the haematological point of view than the absence of the anti-anaemic factor from the gastric juice. It is not within the province of this review to discuss the relationship of this 'intrinsic factor' (Castle) or 'haemopoietin' (Wilkinson and Klein) with pernicious anaemia, but the enzyme appears to be able to function adequately in the absence of hydrochloric acid and pepsin, judging from the behaviour of highly purified fractions already obtained and investigated (Klein and Wilkinson). It is possible that apparently normal individuals with achlorhydria may be able to secrete sufficient haemopoietin to prevent the onset of pernicious anaemia until some sudden and excessive demand is made upon the haemopoietic centres. Such may be the explanation for the occurrence of the pernicious anaemia with pregnancy, the pernicious anaemias of pregnancy (Wilkinson, 1932), and the megalocytic anaemias after gastrectomy and gastro-enterostomy (Wilkinson, 1933).

It appears probable that the achylia gastrica associated with pernicious anaemia has been present for a considerable period—thus cases have been reported in which it has been known to exist from four to twenty-five years prior to the diagnosis of pernicious anaemia (Bie; Connor; Faber and Gram; Haden; Hurst; Hurst and Stewart; Riley; Sturtevant), while no case of idiopathic anaemia has been observed to develop achlorhydria after a previously observed normal gastric secretion. In this connexion it should

be noted that cases of 'secondary' pernicious anaemia have been known to follow cauterization of the stomach by nitric acid (Fleischer-Hansen) or oxalic acid (Hartfall and Witts, 1933) which apparently produced complete artificial achylia, and also after gastrectomy or gastro-enterostomy for carcinoma, ulceration, syphilis, and tuberculosis (Wilkinson, 1933).

A consideration, however, of the so-called primary idiopathic pernicious anaemia as distinct from these 'secondary' pernicious anaemias suggests most strongly a familial or hereditary tendency to the disease. Martius suggested that the majority of cases of achlorhydria were constitutional or primary, although Faber considered that the achlorhydria was secondary to a pre-existing gastritis. Hurst (1932), who has repeatedly drawn attention to the familial incidence of pernicious anaemia and achlorhydria, and Wilkinson and Brockbank, believe that such an hereditary familial condition exists, the gastric mucous membrane failing to secrete hydrochloric acid through an inborn error in development as has already been considered above; the evidence, however, is mainly circumstantial.

In a recent paper Wilkinson and Brockbank (1930) described 139 families in which two or more members were affected with pernicious anaemia with or without the complication of combined degeneration of the cord, fifty-nine families in which pernicious anaemia and achlorhydria existed simultaneously in different members, and seventeen families in which achlorhydria was found without pernicious anaemia. They also found that the occurrence of achlorhydria in relatives of cases suffering from pernicious anaemia differed widely according to different observers; Weinberg found 41·7 per cent., Connor 26 per cent., Wilkinson and Brockbank 23·7 per cent., Zadek 21·7 per cent., Neuberger 3·4 per cent. (one case).

Thus with their own cases Wilkinson and Brockbank collected 70 cases of familial achlorhydria occurring in 291 relatives, which gave an average of approximately 24·1 per cent. It should be noted in passing that half of their own cases actually had achylia. According to Weinberg the achlorhydria occurs at an early age, for he found that in 22 children of 12 patients with pernicious anaemia 9 had achylia, and he described a family in which 3 out of 4 children under 10 years of age had constitutional or familial achlorhydria. It is not easy to get an accurate idea of the frequency of achlorhydria in the relatives of patients suffering from pernicious anaemia on account of the difficulty of obtaining examinations on apparently healthy people, but there is no doubt that it is much commoner than has been previously supposed, and is obviously greater than 24 per cent. of the relatives.

It is noteworthy that pernicious anaemia (with achylia gastrica) occurs with almost equal frequency in both sexes: thus Wilkinson (1933, this volume) found that in his series of 370 cases there were 186 females and 184 males. This is in marked contradistinction to the almost exclusive occurrence of microcytic anaemia with achlorhydria in women (*vide infra*).

Microcytic hypochromic anaemias. During the last few years attention

has been drawn to the frequent association of anaemias of a non-Addisonian type with achlorhydria or achylia. Borgbjaerg and Lottrup (1929), Hartfall (1933), C. Hunter (1923), Hurst (1932), Meulengracht (1932), Morley and Roberts, Schneider and Carey (1928), and Weinberg (1920) amongst others, all noted the occurrence of severe anaemias with low colour indices in their series of achlorhydric or achylic patients.

It was Faber (1909, 1913), however, who first emphasized the nature of the syndrome of 'simple achylic anaemia', which is now known to have such well-defined features. Since then the condition has been fully investigated by a large number of workers who have given to it a variety of names (Kaznelson, Reimann, and Weiner, 1929; Altschüler, 1929; Gram, 1930; Waugh, 1931; Mills, 1931; Dameshek, 1931; Mettier and Minot, 1931; Schülten, 1932). This syndrome of an anaemia of microcytic type with low colour index and associated with achlorhydria or achylia has been very fully and accurately described by Witts (1930). Of similar type is the microcytic anaemia with dysphagia—the so-called Plummer-Vinson syndrome (Kelly, 1919; Paterson, 1919; Vinson, 1922), which is really a dysphagia associated with a chronic microcytic anaemia usually of the simple achlorhydric type, although occasional cases may show the presence of free hydrochloric acid (Cameron, 1929; Witts, 1931; Suzman, 1933).

The frequent occurrence of this microcytic anaemia amongst patients with an achlorhydria, whether congenital or hereditary, or secondary to gastritis, injury, or gastric surgery is so striking that the aetiological significance of the gastric deficiency in the production of anaemia is of great importance. It appears to be fairly certain that the achlorhydria is present before the anaemia, and in common with other observers (Meulengracht, 1932; Hurst, 1932; Hartfall and Witts, 1933) we have often detected the former long before any degree of blood change has been noted.

In pernicious anaemia it has been definitely shown that the important gastric deficiency is the anti-anaemic principle rather than the hydrochloric acid (Castle; Wilkinson and Klein, 1932, 1933). On the other hand, in achlorhydric anaemia the anti-anaemic principle is not entirely absent (Hartfall and Witts; Wilkinson) and the important deficiency appears to be the hydrochloric acid and the pepsin. There must, however, be some close relationship between the two anaemias since one occasionally finds a microcytic achlorhydric anaemia changing over after treatment with iron (sometimes independently of any therapy) into a macrocytic anaemia; the reverse change, however, may occur (Wilkinson, 1933). One of us (Wilkinson, 1933) has had several of this type of case under observation for some years now, and similar ones have been mentioned by Thaysen (1928), Gram (1930), Witts (1930), Hurst (1932), and Hartfall and Witts (1933). It is particularly striking that these changes in type of anaemia are more liable to occur after gastrectomy or gastro-enterostomy in patients in whom the haemopoietic systems appear to be unstable and tend to react excessively

to treatment (Wilkinson, 1933). There is obviously a close connexion between these two anaemias.

In many of these cases of microcytic anaemia there is actually a complete achylia, but in others free hydrochloric acid may sometimes be secreted under the influence of histamine (Witts; Davies and James; Wilkinson; Meulengracht; Hartfall and Witts) or gastric lavage (Hurst, 1932; Hartfall, 1932); clinically, however, the cases are identical.

The dysphagia associated with the Plummer-Vinson syndrome is usually relieved *pari passu* with the anaemia by adequate treatment with iron and hydrochloric acid therapy.

It is important to realize that the gastric deficiency persists even when these microcytic anaemias show the return of normal blood counts, and Hartfall and Witts (1933) refer to this persistence in a number of their cases that were re-examined after as many as seven years.

Wilkinson and Brockbank (1930) have discussed the familial or hereditary tendency for pernicious anaemia to occur in families. It was found, too, in the course of the investigation that a microcytic anaemia was quite commonly present in other members of such families—many with achlorhydria—and the possibility of conversion to pernicious anaemia is open to serious consideration in such individuals. Hartfall and Witts (1933) have also reported cases of familial simple achlorhydric anaemia. Thus the evidence is strongly in favour of the gastric anacidity being a precursor of the simple achlorhydric anaemia. The causes of this achlorhydria have already been discussed above, and it is possible that its greater incidence amongst women may be an important factor in the almost exclusive occurrence of chronic microcytic anaemia in such patients.

The microcytic anaemias of pregnancy are frequently associated with achlorhydria and resemble very closely, or are identical, with the microcytic anaemias described above. On the other hand, the macrocytic or 'haemolytic' anaemias of pregnancy do not show such achlorhydria and this is an important distinguishing feature from pernicious anaemia (Wilkinson, 1932).

The association of anacidity with other diseases of the blood has not been observed to any marked degree. Watson-Wemyss (1911), Parkes Weber (1931), Platt (1932), and Michaelides (1932), have seen achlorhydria in patients suffering from polycythaemia rubra.

The macrocytic anaemias associated with parasitic infestation (dibothriocephalus latus and ankylostoma duodenale) are closely allied to pernicious anaemia (Wilkinson, 1933), showing achylia gastrica and the typical responses after liver and hog's stomach therapy that are seen in pernicious anaemia.

For these reasons attempts have been made to find aetiological factors common to all these anaemias, many observers believing that the gastric and haematopoietic changes are due to toxins or haemolysins produced directly or indirectly by these parasites or bacteria. This is in contradis-

tinction to the view that pernicious anaemia may be of the nature of a deficiency disease.

In this connexion it is important to notice that the two deficiency diseases sprue and pellagra may show clinical pictures very closely resembling pernicious anaemia, particularly with reference to the gastro-intestinal symptoms and the condition of the blood; Guthrie (1932) found that in 476 pellagrins (collected from the literature) on whom gastric analyses were carried out 56·3 per cent. had achlorhydria.

Owing to this resemblance to Addison's anaemia difficulty may occasionally arise in making a diagnosis of pellagra if occurring in non-tropical countries or other geographical positions where it is a rarity. A similar consideration obtains with regard to sprue in which achlorhydria may be frequently found to as much as 50 per cent. according to Castle and Rhoads (1932), although a further 20 per cent. may secrete acid under the influence of histamine.

Achlorhydria and Subacute Combined Degeneration of the Spinal Cord

The secretory functions of the stomach in subacute combined degeneration without anaemia have received relatively little attention; associated with pernicious anaemia, however, it has been more fully investigated and shown to be associated with achylia gastrica. Hurst and Bell first considered the question in any detail, finding a similar gastric anacidity in postero-lateral sclerosis without anaemia. Since then Hurst (1928) has reinvestigated and added to his original cases, reporting achylia by fractional gastric analysis in 35 cases. In the same paper he refers to 57 other cases examined by the Ewald and fractional methods that he has collected from the literature. Apparently one of the first was reported by Faber (1898). The only other relatively large series were Vanderhoof's 29 cases and the 44 of Ungley and Suzman, all with achylia gastrica. We have already considered (*vide supra*) the association of pernicious anaemia with achylia, including such cases showing in addition postero-lateral involvement of the cord. One of us (Wilkinson) has examined 39 cases of subacute combined degeneration without anaemia, and the results of the fractional gastric analyses in this small series fully confirm the findings of other observers that achylia gastrica occurs in 100 per cent. of such cases; in no case has undoubted postero-lateral sclerosis of the spinal cord been found to be associated with free hydrochloric acid in the gastric juice. The finding of free hydrochloric acid should accordingly suggest caution in accepting such a diagnosis. It is interesting to recall in this respect the experimental work of Gildea, Kattwinkel, and Castle, in which changes were produced in the spinal cords of animals resembling the human subacute combined degeneration of the spinal cord by the feeding of diets deficient in the antineuritic fraction of vitamin B. In none of these experiments, however, did they observe any significant changes in the gastric secretions.

The Endocrine System

Moll and Scott examined 50 cases of Graves' disease with the Rehfuss meal, 22 had achylia, while the average duration in the achlorhydric cases was 2·9 years, the hypo-acidic 1·1 years, and the normals 0·5 year. They suggested that the achlorhydria occurred in the course of the disease and was not a predisposing cause. Of the cases of achlorhydria they found that 60 per cent. were due to a duodenal regurgitation. They believed that the lowered secretion could be explained by a twofold mechanism: (*a*) associated with overaction of the vagus, causing hastening of the gastric contents, and duodenal regurgitation, producing an apparent achlorhydria, and (*b*) a direct inhibitory action of the sympathetic on hydrochloric acid secretion, causing a true achlorhydria.

Meulengracht (1932) observed 4 cases of exophthalmic goitre with achylia gastrica, while Friis-Möller found that 17 out of 24 cases had achylia or hypo-acidity. Achlorhydria was also seen by Moore in 78·7 per cent. of his cases with hyperthyroidism, and by Faber in 50 per cent. with Graves' disease. Lerman and Means noted 38 per cent. with achlorhydria in their cases of Graves' disease, and 53 per cent. in the myxoedematous cases. In the former there appeared to be a correlation between the incidence of achlorhydria and the basal metabolic rate, while they noted a tendency to anaemia in those with myxoedema and achlorhydria. From an investigation of 35 patients with exophthalmic goitre, using histamine, Berryhill and Williams found 24 (69 per cent.) were achlorhydric and 8 had hypo-acidity, while in 15 cases of adenoma with an increased basal metabolic rate 10 had achlorhydria and only 5 hypo-acidity. Neither age nor the duration of the disease appeared to have any influence, and they could find no correlation with the elevation of the metabolism; 38 per cent. of these patients had severe gastric symptoms—anorexia, vomiting, diarrhoea, and abdominal discomfort. In 26 of the achlorhydric cases which they were able to follow up for six months after thyroidectomy, 80 per cent. of those with exophthalmic goitres and 50 per cent. of those with toxic adenoma showed a gradual return of acidity, which was found at first only after the use of histamine. They believe that thyroid over-activity may play the major role in producing a diminution of secretion of acid. In 9 adenomatous goitres without increase of metabolism there was a normal acidity.

It is of interest in this respect that Thomsen was also able to diminish markedly the gastric acidity in dogs by the administration of thyroid extract, and discontinuance of this permitted the acidity to return to normal: he did not observe the production of gastritis, and considered the effect to be a toxic one upon the gastric mucosa.

Diseases of the Pancreas

Chronic pancreatitis and carcinoma may occur in conjunction with achlorhydria, while diabetes mellitus is by no means uncommon. Bowen and Aaron

investigated 69 cases of diabetes mellitus and found achlorhydria in 20 (29 per cent.); 35 per cent. of their cases with achlorhydria died. They did not find it in mild cases or in patients who had had the disease for less than a year, nor did they find diarrhoea in any patient unless achlorhydria also existed. They suggested that in diabetes there was an abnormality of the whole of the digestive system, and that achlorhydria was the result of long standing or severe diabetes. We also have found achlorhydria in a considerable number of diabetics, and in them have found an abnormal sensitivity to insulin, an observation which they too have noted.

In one case under our care, treatment with insulin was only satisfactory when it had been found that the patient's father had died of pernicious anaemia, which led to the discovery of an anacidity and its subsequent treatment by hydrochloric acid. Moore found 39·7 per cent. with achlorhydria (13 males, 20 females), and noted that glossitis and gastro-intestinal symptoms were rare in diabetics. Joslin saw 27·3 per cent. with achlorhydria in 106 cases, and Rabinowitsch, Fowler, and Watson 39 per cent. in 100 cases of diabetes mellitus.

Rheumatoid Arthritis

The association of gastric anacidity with rheumatoid arthritis has been noted for many years. Faber (1913) found achylia gastrica in 15 out of 65 patients with chronic polyarthritis, and drew attention to the anaemia which was often present in these patients; the latter symptom he believed to be a sequela of the achylia. Borries showed that 30 per cent. of 94 cases of arthritis had achylia as shown by the Ewald test meal, Gram (1921) noted the association, and Coates and Gordon found achlorhydria in 14 out of 20 cases using this test. They think it is the crucial factor in the whole clinical picture. Woodward and Wallis made similar observations, while Miller and Smith, from a study of 250 cases, came to the conclusion that achlorhydria and hypochlorhydria were five times as great as in normal subjects, but only slightly greater than in all other diseases; but that chronic arthritis, not definitely associated with sepsis, was more often accompanied by achlorhydria.

On the other hand, Lottrup recently described a series of cases of chronic progressive polyarthritis, in which 44 per cent. had achylia and 58 per cent. a simple anaemia; in other forms of arthritis he found only 11 per cent. achylia and 34 per cent. of anaemia. He says the anaemia is of the simple type, is usually slight, and found more frequently in those patients who are also the subjects of achylia. Jansen also drew attention to the anaemia, and believes it was dependent on the duration of the arthritis, but did not discuss its relationship to achlorhydria. Hartfall found 30 per cent. of his cases with rheumatoid arthritis had achlorhydria, and it was also present in 11·3 per cent. of cases with severe fibrositis. In 37 cases examined by one of us (J. F. W.), 11 had achylia gastrica and 8 hypo-acidity, but many of these cases were selected for examination either because of recurrent diarrhoea or a sore tongue; these improved in health after acid therapy, although the

joint symptoms showed little amelioration, since all were advanced cases. The presence of digestive disturbances, anaemia, or a sore tongue in rheumatoid arthritis strongly suggests the possibility of gastric secretory impairment, and a gastric analysis should be made if any of these be present. It is possible, however, for these patients to have an achlorhydria without any of these symptoms, and in our cases the analyses were made as a matter of routine. Although most investigators emphasize the importance of impaired gastric secretion in rheumatoid arthritis, it should be noted that Eggleston does not feel that achlorhydria is a definite factor. It is possible, of course, that the high figures obtained by some clinicians may be due to the employment of the Ewald one-hour test meal.

Achlorhydria in Allergic and Skin Diseases

In diseases of *allergic origin* there appears to be a high frequency of either achlorhydria or hypochlorhydria. Thus Criep and McElroy in studying 50 cases of asthma, hay fever, urticaria, angioneurotic oedema, and atrophic rhinitis found achlorhydria in 36 per cent., a complete achylia in 4 per cent., and hypo-acidity in 32 per cent. There was only one case of migraine in their series and this showed a hypo-acidity. Schneider and Carey (1928) reported similar findings. Hartfall (1932) also found achlorhydria in both migraine and asthma cases. Rowe, while advocating the importance of the treatment of achylia in allergic migraine, if it has been found to be present, said that this will not in itself relieve symptoms if the offending foodstuff has not already been eliminated from the diet. In 80 cases of gastro-intestinal allergy he found achylia in 10 per cent. Beckman gives acid in big doses in the treatment of allergic diseases; according to him, the supply of acid-forming substances in the blood of these subjects is not high and there is thus a tendency to hypochlorhydria or achylia because the blood has so little acid-forming material to spare. He quotes the Walzers, who found that urticaria was accelerated by hypochlorhydria and retarded by hyperchlorhydria. Wilkinson and Brockbank (1930) record a case of pernicious anaemia in which an urticarial rash was produced by liver diet and was prevented by the use of hydrochloric acid. Studying asthma in childhood Bray (1931) found a diminished secretion in these subjects as compared with normal children, the deficiency of secretion being more frequent below the age of seven. Sex had no influence, but the usual rise of acidity at puberty did not occur as frequently in girls as in boys, and he suggested that the tendency for asthma to persist in women was due to this. Fifty per cent. of the parents of asthmatic children showing some allergic symptoms had a deficiency of hydrochloric acid, and he thought the tendency to allergy was transmitted twice as often through the mother.

Other dermatoses which have not been shown definitely to be of allergic origin are frequently associated with anacidity. Ryle and Barber found that in 12 cases (all females) of rosacea 5 had an achlorhydria and 2 hypo-

acidity. Similar results have been obtained by Brown who examined 50 cases of rosacea and found that 7 had achlorhydria and 8 hypochlorhydria in the first group; in a group of 50 other dermatoses he noted 6 and 5 respectively. Rulison has also observed achlorhydria in 14 per cent. of 50 cases of rosacea and noted the frequent association of functional abnormalities, neurosis, subnormal weight, poor muscular tone, visceroptosis, but constipation rather than diarrhoea. Stein has reported similar findings. In an examination of 19 cases of psoriasis, Ayres found 52 per cent. with diminished or absent gastric acidity, while one of us (Wilkinson) has found that in 100 cases of psoriasis there were 16 per cent. with achlorhydria or achylia and 30 per cent. hypo-acidity, many responding to hydrochloric acid therapy.

Treatment of Achlorhydria

The treatment of achlorhydria falls into two groups. In the first an attempt is made to induce the impaired gastric mucous membrane to secrete hydrochloric acid again, and in the second the deficiency is remedied by the giving of adequate doses of hydrochloric acid and pepsin. The former method is advocated by Hurst, and he has had successful results after repeated lavage with a solution of hydrogen peroxide. Obviously this method is of no use in cases due to a complete achylia, and he uses it only when he believes the lack of acid is due to a chronic gastritis.

If an attempt be made to correct the deficiency by the administration of hydrochloric acid and pepsin it is necessary to use an adequate dose. Crohn showed that small single doses of hydrochloric acid (U.S.P. dil. 11·5 per cent.) were neutralized when given to achlorhydric patients and at least 1·6 to 2·6 c.c. were required to render the gastric contents acid. Kern, Rose, and Austin found doses of 4·8 c.c. of dilute hydrochloric acid (U.S.P.) adequate and preferable to the usual dose of 1 c.c., but the long continued administration of hydrochloric acid did not stimulate the secretion of pepsin nor effect the spontaneous appearance of hydrochloric acid. Shaw (1924), Vanderhoof (1923), and Hurst have reported similar findings, and the former states that doses of 10 minims are useless. On the other hand, Leo said that 2·5 c.c. of hydrochloric acid produced free hydrochloric acid in gastric juice while larger doses (12 c.c.) failed to do so.

We find that 30 minims of the dilute hydrochloric acid of the British Pharmacopoeia are usually sufficient combined with i–ii drachms of glycerinum pepsini (Wilkinson and Brockbank).

Sansum and Gray advocate the use of citrus fruits (lemons and grapefruit) in preference to dilute mineral acids and report good responses. The results obtained vary according to whether there is an associated organic lesion. In the functional cases with dyspepsia and diarrhoea the results are usually very satisfactory and, generally speaking, those cases showing complete achlorhydria are more likely to do well than those showing only a hypo-acidity.

In patients with organic disease the general health is often improved, and thus the treatment of such conditions as diabetes, hyperthyroidism, and rheumatoid arthritis is facilitated. In the microcytic anaemias hydrochloric acid is said to improve the response to large doses of iron through aiding the absorption of the latter. In the treatment of pernicious anaemia its use is invaluable for the relief of the frequently distressing gastro-intestinal symptoms that may otherwise persist when the liver diet is employed. On the other hand, it does not appear to be necessary when hog's stomach therapy is used (Wilkinson, 1930, 1931, 1932).

Cases of allergic disease with achlorhydria often show a striking improvement. In all these, however, the administration of hydrochloric acid should be regarded as a part and not the whole of the treatment.

Cases of glossitis may clear up completely, but treatment in these cases is often difficult owing to the soreness of the tongue. The condition usually returns when the acid is discontinued (Wilkinson and Oliver).

Summary

1. Achlorhydria is more common in women than in men.

2. While achlorhydria is common the use of histamine has shown that achylia is rare, except in cases of pernicious anaemia.

3. It may occur in apparently healthy subjects, but it is rare in those who are completely normal, and it may be the forerunner of disease developing many years later.

4. There is a strong hereditary or familial tendency to the condition and a family history of anaemias, allergic disease, or rheumatoid arthritis is frequent.

5. Achlorhydria may occur at any age, but is more common in later life.

6. Its aetiology may be (*a*) familial, due to a constitutional abnormality, (*b*) due to chronic gastritis either from direct irritation or from a haematogenous intoxication, and (*c*) of neurogenic origin.

7. It is common in debilitating diseases, especially tuberculosis, malaria, and chronic colitis.

8. It occurs frequently in association with certain functional disturbances, neurasthenia, flatulence, irregularity of the bowels, debility, slight anaemia, and disturbances of the tongue.

9. The association of two or more of these symptoms may produce a clinical picture which has hitherto been diagnosed as a neurotic dyspepsia but which we believe should be regarded as a syndrome of achlorhydria. This syndrome is often associated with rheumatoid arthritis or some allergic manifestation.

10. Achlorhydria is often associated with organic disease of the gastro-intestinal tract, chronic gastritis, gastric and intestinal cancer, colitis, and dysentery; of necessity it follows total gastrectomy, but it may or may not follow partial gastrectomy or gastro-enterostomy.

11. It has been looked upon as evidence of chronic gastritis, which in turn has been regarded as a precursor of cancer of the stomach. The sex incidence and the infrequent combination of the achlorhydric anaemias with cancer suggest that it is not an important aetiological factor.

12. Achlorhydria is very rare in duodenal ulcer but less uncommon in gastric ulcer. When it occurs it is probably the result of a secondary chronic gastritis.

13. Severe pain occurs in some cases of achlorhydria and may resemble that of ulceration. X-rays have shown the presence of an increased gastric and intestinal motility and of pylorospasm which probably accounts for this symptom.

14. Achlorhydria is frequent in cholecystitis and diseases of the liver.

15. It is an almost constant accompaniment of pernicious anaemia and of subacute combined degeneration of the spinal cord.

16. It is frequently associated with the microcytic anaemias.

17. There is evidence to show that the absence of hydrochloric acid is not the main aetiological factor in pernicious anaemia but may be an important factor in the development of the microcytic anaemias.

18. Achlorhydria is common in hyper- and hypothyroidism and in diabetes.

19. It occurs in rheumatoid arthritis and should be looked for especially in patients suffering from this disease who exhibit symptoms of diarrhoea, glossitis, or a slight anaemia.

20. It is common in allergic disease, asthma, migraine, urticaria, and in dermatoses such as rosacea and psoriasis which have not been shown to be of allergic origin.

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THE HYPERTENSIVE CEREBRAL ATTACK [1]

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For the proper understanding of the cerebral symptoms in arterial hypertension it will be necessary to consider the modern conception of uraemia, which holds that changes in the blood chemistry are an essential feature and that many of the cerebral symptoms, formerly grouped under this heading, occur in the absence of nitrogen retention. Volhard (16) divides the so-called uraemia state into acute and chronic pseudo-uraemia and true uraemia. He emphasizes the fact that the pseudo-uraemic conditions may occur in the absence of renal insufficiency. Acute pseudo-uraemia is always accompanied by raised intracranial pressure and clinically by headache, vomiting, and bradycardia. The brain volume is increased owing to oedema. This oedema occurs as the result of an acute disturbance of the circulation in the brain which leads to increased vessel permeability. Vasoconstriction is not a necessary precursor of this condition. As the result of the oedema, localized anaemia of individual parts of the brain may occur, giving rise to convulsions, local or generalized, bilateral amaurosis, &c. He cites eclampsia as a typical example of acute pseudo-uraemia. In chronic pseudo-uraemia the factor of vessel contraction is the important one and leads to ischaemia. The dividing line, however, between the acute and chronic forms is not sharp; the one may pass into the other, or both may be present at the same time. A raised blood-pressure is the determining factor in both forms. He mentions the phenomena of dead fingers and of intermittent limping as examples of spasm of peripheral arterioles. He believes that the transient focal symptoms are similarly caused by spasm of the corresponding cerebral vessels, that it is thus a question of angiospastic aphasia, hemianopia, paralysis, and convulsions. According to this conception the pseudo-uraemic cerebral symptoms are caused by local anaemia of the brain. 'In the chronic form we are dealing, not with acute hypertension in thin-walled young vessels whose permeability is apparently increased, but with cases of chronic hypertension, which have suffered for years from raised blood-pressure and have thickened vessels.' He further states that the local vessel spasms are probably determined by arteriosclerotic changes in the larger vessels. As a rule, the rise in blood-pressure is the factor which

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excites spasm in arteriosclerotic or hypertensive vessels. In true uraemia the symptoms are due to the toxic phenomena of nitrogen retention and acidosis, the result of renal insufficiency. The complexion is greyish-yellow in contrast to the simple pallor which is not even constantly observed in cases of pseudo-uraemia. There is a loss of flesh and mental dullness. Muscular twitchings may occur, but no convulsions or focal cerebral signs. Breathing is often deep. Anorexia and vomiting are marked. There may be retention of consciousness until near the end, or the patient may lapse into coma.

Blackfan (3) has recently studied the etiology of cerebral symptoms in acute glomerulo-nephritis in a group of children. Headache, vomiting, visual disturbance, coma, and convulsions were the symptoms indicating so-called uraemia. He noted that concurrently with a rise in blood-pressure the cerebral symptoms appeared, and that the latter were independent of the amount of non-protein nitrogen in the blood and the degree of haematuria and anuria. In every case he found a raised cerebrospinal fluid tension by manometric readings. The cerebral symptoms were relieved by intravenous injections of magnesium sulphate and at the same time the blood-pressure fell. He concluded that the arterial hypertension is, partly at least, the result of increased intracranial pressure and that this is caused by oedema of the brain. Oppenheimer and Fischberg (10) stress the fact that the cerebral episodes in hypertension are generally preceded by an additional rise in blood-pressure above the previous high level. They give the name 'hypertensive encephalopathy' to the cerebral symptoms occurring in hypertensive states. They find that the common factor in eclampsia, acute lead poisoning, glomerulo-nephritis, and essential hypertension is a raised blood-pressure and that the cerebral symptoms are the same in these conditions. They believe that these symptoms are brought about by vasoconstriction of the cerebral vessels. This theory of vasoconstriction of the cerebral vessels, so ably upheld by Volhard, is not new and was favoured by Osler (11) and others.

In this country the majority of physiologists still hold the view, based on the experimental work of Roy and Sherrington (14), Bayliss and Hill (1), Hill and Macleod (8), that the cerebral vessels are not under vasomotor nervous control. On the other hand, workers, especially in other countries, have added evidence in support of the existence of a nervous control of the pial vessels. This problem, however, which is obviously of great clinical importance, does not seem to have reached a conclusive stage at any one observer's hands until the work of Forbes and Wolff (6) in America. The previous workers had used one of two experimental methods, (i) the recording of pressure under varying experimental conditions, (ii) the direct observation of blood-vessels on the surface of the brain through an opening in the skull. Forbes (5) has elaborated a method by which both of these procedures are possible. Direct observation as well as photography of the pial vessels was made possible through a specially devised tight window in the skull of

the cat; at the same time records of the intracranial and intravascular pressures were made by means of suitable manometers. Forbes and Wolff, using this method, have demonstrated beyond all reasonable doubt, by using controls and taking precautions against errors, that the pial vessels in the cat possess an efficient vasomotor control. A summary of their experiments must suffice, but these should be read in the original by all those who are interested in this important subject. (i) Stimulation of the cervical sympathetic in the neck by faradic current was followed by constriction of the arteries in the pia in each of the twenty-three animals examined. In the great majority of the experiments there was no accompanying fall in blood-pressure, so that this could be eliminated as a factor in the resulting vaso-constriction that took place. (ii) Stimulation of the vagus in the neck was followed by dilatation of the pial arteries in twelve of thirteen animals examined. A sudden and even striking fall in general systemic arterial pressure occurred in almost every case. (iii) Local irrigation of the pia with an epinephrine solution was followed by constriction of the pial arteries without any effect on the general arterial pressure. On the other hand, intravenous injections of the same substance often caused a considerable rise in systemic arterial pressure and coincidently a dilatation of the pial arteries; when the blood-pressure began to fall a true constriction of the pial arteries was noted.

Using the same methods, other experiments were carried out in order to ascertain the effect on the pial vessels of changes in the chemical composition of the blood. The results may be shortly summarized as follows: constriction of the pial vessels resulted from (i) intravenous injections of hypertonic solutions, (ii) a decrease in the carbon-dioxide content or an increase in the oxygen content of the blood, (iii) intravenous injections of pituitrin. Dilatation of these vessels followed from (i) an increase in the carbon-dioxide content of the blood or a state of anoxaemia, (ii) a condition of acidosis, (iii) inhalation of amyl nitrite (Wolff and Forbes (20), Wolff (19), Wolff and Lennox (18)). The results of these experiments suggested that the chemical composition of the blood plays an important part in the regulation of the intracranial circulation, and that they may throw light on such problems as headache, convulsions, &c.

Further proof of a true nervous control of the pial vessels has been provided by recent histological research. The work of Stohr (15), Hassin (7), and of Penfield (12) may be referred to, as they used modern methods of staining. Stohr employed material from human embryos and also the brains from executed criminals which he was able to obtain half an hour after death. By using Schultz's modification of Cajal's silver method he was able to demonstrate clearly the existence of nerve-endings in all vessels of the pia and choroid plexus. He believed that the nerves to the pial vessels are derived partly from the carotid and vertebral plexuses and partly from fine branches given off by the 3rd, 6th, 9th, 10th, and 11th cranial nerves. The vascular innervation is, therefore, both sympathetic and parasympathetic.

Hassin, using similar staining methods, has been able to confirm Stohr's observations. He found nerve-fibres mainly unmyelinated in the blood-vessels of the pia but none in the vessels of the cerebral tissues proper. Penfield, employing a modification of the Gros-Bielschowsky method, has shown that not only do the pial vessels possess nerve-fibres, but so do the intracerebral and intramedullary arteries.

The effects of arterial spasm have been considered by a number of writers. It will be sufficient here to refer to the papers of Ricker (13), and Westphal and Bar (17). Ricker, as a result of animal experimentation, found that when an artery became extremely contracted through some instability of its nervous control there followed a dilatation of its capillaries with slowing of the blood-stream through them, and that diapedesis of red cells through the capillary walls might follow. In this way considerable extravasation of blood may occur, resulting in necrosis of the parenchyma in the neighbourhood. The process may react on the vessel walls in its vicinity causing necrosis and further haemorrhage. Westphal and Bar, in a study of the small haemorrhages which occur in the neighbourhood of an apoplectic focus in the brain, found not only sclerosis of arterioles and arteries but, especially, necrosis of the walls of small vessels with numerous small haemorrhages around them. They considered that these changes might be due to arterial spasm in cases of hypertension. When the spasm passes off, the blood flows into vessels whose walls have become altered and diapedesis of red cells takes place. We are too apt to think of cerebral pathology in arterial hypertension in terms of thrombosis or massive haemorrhage. Ricker's theory and its modifications would seem to throw light on certain cases of hemiplegia and others showing focal signs which clear up rapidly, and which we usually attribute to thrombosis.

These experimental and histological researches seem to prove the existence of a nervous control of the blood-vessels of the pia, and in all probability of the brain itself. From this it may be assumed that the supply of blood to the brain is dependent on the state of tonus in the cerebral arteries and arterioles, which in its turn is influenced by impulses received from the sympathetic and autonomic nervous systems. The cerebral vessels will respond to any disturbance of the normal balance existing between these two systems, whether this be temporary or permanent, in the same manner as the blood-vessels in other parts of the body, and also to changes in the chemical composition of the blood. These facts would readily explain such conditions as migraine, epilepsy, and certain of the cerebral symptoms of arterial hypertension.

Volhard uses the term 'acute pseudo-uraemia' and Oppenheimer and Fischberg 'hypertensive encephalopathy' to describe the acute cerebral symptoms that may occur in arterial hypertension. The term 'hypertensive cerebral attack' is suggested, owing to its greater simplicity.

These attacks may take one of two forms, depending on the presence or absence of cerebral oedema.

The Hypertensive Cerebral Attack with Signs of Cerebral Oedema

The patient is usually under the age of forty, and may be a child suffering from acute nephritis, or an adult with raised blood-pressure either primary in type or secondary to an old nephritis. The sudden appearance of severe headache is the characteristic feature of these attacks. The headache may be frontal or occipital; it may last for several days and it is often accompanied by vomiting, cerebral in type. Drowsiness, amounting in rare instances to coma, is commonly present. Epilepsy, generalized or Jacksonian, may rarely usher in the attack. Motor weakness with focal signs or loss of vision may be temporarily present during the attack. Ophthalmoscopic examination almost invariably shows evidence of a hypertensive retinitis (9). The earliest change that may be observed is a constriction of the retinal arterioles. The degree of constriction varies from time to time and a single artery may show considerable variation in calibre throughout its course. Haemorrhages, exudate, and papilloedema make their appearance within a few hours. In rare cases, of which I have seen several instances, papilloedema may be the only obvious change on ophthalmoscopic examination. This finding, in conjunction with severe headache and vomiting, may suggest a diagnosis of cerebral tumour. The outstanding feature in these attacks is the rise in blood-pressure. In young persons the pulse-pressure is comparatively small and, therefore, particular attention should be paid to the diastolic pressure which may reach a figure of 160. The cerebrospinal fluid pressure is raised; with Greenfield's manometer figures exceeding 250 mm. of water are not uncommon. A marked degree of papilloedema is always accompanied by a high cerebrospinal fluid-pressure reading. In acute nephritis the changes in the urine will be characteristic of that condition. In the remaining cases albumin in the urine is a constant finding, whether the case be one of primary hypertension or a form of chronic nephritis. The presence of casts and red cells may not necessarily be indicative of true nephritis. The nitrogenous products in the blood are within normal limits, unless uraemia is a complicating factor.

Case 1. E. L., female, aged 24, was admitted to the Middlesex Hospital under Dr. D. E. Bedford on October 20, 1931, to whom I am indebted for permission to examine her and report the case.

Apart from an occasional headache, especially at the menstrual period, she felt well until June 1931 when the headaches became rather more severe, but she was able to continue with her work. On July 3 she had a severe frontal headache and vomited. At the same time she experienced a 'pins and needles sensation' in the hands and feet, more especially in the former, which lasted for about fifteen minutes. On the same day the vision in the left eye became blurred. On two subsequent occasions similar attacks occurred. Since July, for the first time, there had been nocturnal frequency of micturition. During the same period she had lost ten pounds in weight. No history of scarlet fever or tonsillitis was elicited.

She appeared to be of an emotional type. The cheeks and mucous membranes were well coloured. There was moderate hypertrophy of the

left heart. The radial artery was easily palpable. Blood-pressure 220/150. A well-marked bilateral hypertensive retinitis was present with approximately 5 diopters of papilloedema. The retinal arteries were markedly constricted. The cerebrospinal fluid pressure was 280–90 mm. of water. No oedema of the subcutaneous tissues was present. There was considerable albuminuria, with occasional red cells and a few hyaline casts. Blood-urea was 26 mg., non-protein nitrogen 26 mg., and cholesterol 250 mg. per 100 c.c. Urea clearance test gave a figure equal to 36 per cent. of normal. After several weeks in hospital she was discharged free from headache with considerable resolution of the retinitis and with a trace of albumin in the urine. She has since gained 1½ stone in weight and has returned to work. When seen in April 1933 she stated that she was entirely free from headaches, except on rare occasions. The gain in weight had been maintained despite daily work in a factory. The ophthalmoscopic examination showed indefinite edges to both disks but no measurable papilloedema. In each macula there were scanty remains of a star-shaped figure. The arteries were somewhat constricted and now showed definite evidence of arteriosclerosis. Blood-pressure 275/160. Urine: Specific gravity 1020, no albumin or casts.

Case 2. R. T., aged 29, was admitted to the Neurological Ward of the Middlesex Hospital on March 20, 1931. He had been well until March 1, 1931, when he had a 'bilious attack' which was characterized by severe headache behind both eyes and at the back of the neck, accompanied by vomiting. On the following days the headache persisted, being especially marked in the morning; it was usually accompanied by vomiting. His eyesight became 'misty'. On March 6 his legs suddenly gave way and he fell to the floor. He did not lose consciousness and his limbs were not convulsed. He regained the power of his legs in three or four minutes, but there followed a 'stiff painful feeling' in the calf of the left leg. He had never suffered from nycturia. There was no history of scarlet fever or recurrent tonsillitis.

He appeared to be a healthy, well-built man without any obvious anaemia. There was no evidence of recent loss of weight. The heart was moderately hypertrophied. Daily blood-pressure readings ranged between 235/160 on admission and 190/120. There was bilateral papilloedema (about two diopters of swelling) with peripapillary oedema and a certain amount of retinal oedema. The veins were much engorged. The arteries were constricted and there was considerable nipping of the veins at the arteriovenous crossings. A few haemorrhages were seen. There was exudation in the form of small white dots and a few larger patches with somewhat hard edges.

Beyond a general increase in the deep reflexes nothing abnormal was noted in the nervous system. There was no oedema of the subcutaneous tissues. Blood W.R. was negative. The cerebrospinal fluid pressure was 180 mm. of water. The urine contained varying amounts of albumin up to 1·9 grm. per litre. A few red cells and hyaline casts were present. Blood-urea 42 mg. non-protein nitrogen 35 mg. per 100 c.c.

The headaches were relieved by lumbar puncture. The blood-pressure did not fall appreciably, and on his discharge on April 13 the figures were 215/140. For his subsequent history I am indebted to Dr. R. C. Shepherd of Boston. On returning home he improved, and later, against advice, insisted on returning to his work, which was that of a fisherman. On July 13 he rose at 4 a.m., cycled six miles, and fished all day until he got caught in a thunderstorm. Diarrhoea set in with severe headache and uncontrollable vomiting, dimness of vision, and later delirium lasting two days followed by

coma and death on July 27. During this time he had haematuria and dysuria.

That the cerebral symptoms in these two cases were merely the local expression of a widespread and severe disturbance of the general circulation is shown by the occurrence of concomitant retinal and peripheral angiospasm. In neither of these cases was there any evidence of retention of nitrogenous products in the blood soon after the onset of the headache. In both cases the blood-pressure was greatly raised, and it is reasonable to assume that the symptoms of cerebral oedema as well as those indicating circulatory disturbance in the fundi and extremities were brought about by the direct effect of a sudden rise in blood-pressure.

The clinical picture may suggest a spontaneous subarachnoid haemorrhage from a 'leaking' aneurysm. Actually such a haemorrhage may take place, but this is due to the rupture of an arteriosclerotic vessel. Recently a woman of 25 was admitted under my care in a state of coma with a typical history of a 'leaking' aneurysm. Blood was present in the cerebrospinal fluid. At autopsy no aneurysm was found, but generalized arterial and arteriolar disease was present. The kidney showed changes typical of ischaemic nephritis. In the following case a picture of a leaking aneurysm was simulated.

Case 3. C. H. L., male, aged 57, had enjoyed good health until the age of 54, when he began to suffer from headaches which became increasingly severe. On the morning of June 21, 1931, on waking he 'did not feel too bright'. In the evening on rising from a chair he was seized with a 'tremendous pain in the back of the neck'. Soon afterwards he vomited and the vomiting was repeated during the night. The pain spread down the back of the neck to the shoulders and between the shoulder blades. On the following day he was seen by Dr. Norman McLennan and Dr. A. E. Thompson, to whom I am indebted for notes on his condition. 'The signs suggested meningitis. The right plantar response was extensor and the left uncertain. There was bilateral papilloedema, more marked in the right eye, with exudate around the disks. Two haemorrhages were seen in the right retina. Arteriosclerotic changes were definite. The blood-pressure was much raised, the highest figure recorded being 242/136. Blood W.R. was negative. The cerebrospinal fluid was normal. An estimation of the blood-urea and examination of the urine gave no definite information. The gradual diminution of symptoms on the decrease of blood-pressure left no doubt in our minds that the hyperpiesia was responsible for his symptoms.' He was seen by me on September 21, 1931. Since his illness he stated that he had been troubled with occasional headaches. At times he had felt 'muzzy-headed' and his memory had not been so good. During the acute illness he had suffered from nycturia, but not before or since. The main points on examination were as follows:

There was definite retinal arteriosclerosis, but no haemorrhages or exudate were seen. The disks were flat, but their edges were slightly less distinct than the normal. There were signs indicating hypertrophy of the left ventricle. The radial and brachial arteries were definitely thickened and tortuous. Blood-pressure 210/120. Beyond a slight exaggeration of the

deep reflexes on the right side with a diminished abdominal reflex on the same side there were no abnormal physical signs in the central nervous system. The specific gravity of the urine was 1018. It contained no albumin or sugar.

Up till the present time he has led a restricted life and has remained free from any major symptoms.

The Hypertensive Cerebral Attack without Signs of Cerebral Oedema

The patient is usually between the ages of 40 and 65, contrasting with the previous type which occurs commonly in younger persons, and has suffered from hypertension for a number of years. The outstanding feature of this form of attack is the occurrence of epileptiform convulsions. Cerebral symptoms such as headache, temporary attacks of aphasia or weakness in a limb, or even a hemiplegia, may have occurred previously. In other cases, however, the patient has been free from such symptoms. In some cases there is no warning of the attack; in others it is preceded by a severe headache or some minor angiospastic symptom such as aphasia. The patient suddenly becomes unconscious and the various stages of the classical attack of epilepsy are passed through. In some cases consciousness returns after a few minutes; in other cases, however, coma persists for one or more days, and during this time there may be further epileptiform attacks, but not infrequently the duration of the coma seems to be out of proportion to the number of fits. Instead of being generalized the attack may take a local or Jacksonian form, in which case consciousness may be retained. The findings in the central nervous system during the course of the attack differ in no way from those usually observed in a case of idiopathic epilepsy, bilateral extensor responses being the rule. Papilloedema is absent and on lumbar puncture the cerebrospinal fluid is not under increased pressure.

The most significant finding is a high blood-pressure reading, which is not due to the actual epileptiform attack, as a reading taken during the state of coma will show. The urine may contain albumin in varying quantities. The blood-urea and non-protein nitrogen figures are within normal limits, provided uraemia is not a complicating factor. Consciousness is regained with a fall in blood-pressure. As a rule no organic signs in the central nervous system remain; however, in other cases, hemiplegic signs of varying degree may persist. These attacks of epilepsy may occur at intervals and are sometimes regarded as cases of idiopathic or senile epilepsy. It is noteworthy that they seldom occur at night. Their appearance late in life with a negative Wassermann reaction and the existence of a raised blood-pressure between the attacks proclaims their relationship to arterial hypertension.

Case 4. A medical man, aged 61, was seen in consultation with Dr. T. Izod Bennett, to whom I am indebted for permission to refer to his notes on the case.

The patient's previous health had been good apart from three attacks of pleurisy in 1897 from which he made a good recovery. In the summer of

1930 he began to experience occasional difficulty in finding the right word when speaking. On December 25, 1930, he had a severe attack of this kind during which he was unable to talk, and at the end of half an hour he lost consciousness and had a series of epileptiform attacks. He recovered at the end of an hour. Right-sided facial weakness and slurring of his speech were noted for a few days. His urine contained a trace of albumin and he was informed that his blood-pressure was 'raised'. After a holiday he resumed work at the beginning of 1931. On February 12, 1931, he had another severe attack with coma and convulsions. He had no recollection of events during about ten days at this period. After a short holiday he returned to work feeling well. During September 1931 he had one severe attack of temporary aphasia. Apart from a history of migraine in his youth, he had been singularly free from headaches.

He was admitted to the Middlesex Hospital in December 1931 under the care of Dr. T. Izod Bennett. He showed no lack of facial expression. His memory on the whole seemed good. There was no evidence of motor aphasia. No localizing signs were found in the central nervous system. The jaw-jerk was not increased, the deep reflexes in the limbs were moderately increased but were equal on the two sides. The plantar responses were bilaterally flexor. The fundi were normal apart from a mild degree of retinal arteriosclerosis. There was no evidence of an old retinitis. The brachial and radial arteries were easily palpable. There were signs of hypertrophy of the left ventricle. Blood-pressure 220/115 on admission, later it fell to 190/105.

The urine contained a trace of albumin. A concentration test showed the highest specific gravity to be 1022. Blood-urea 30, non-protein nitrogen 34, calcium 10·2 mg. per 100 c.c.

This patient died early in 1933 as a result of sudden cardiac failure.

There was no history of epilepsy in this patient prior to the age of 60. Although no blood-pressure figures taken immediately following one of his attacks were obtained, there is at least evidence of cerebral angiospasm as shown by the attacks of motor aphasia. Uraemia, as an explanation of the attacks, can be dismissed. The patient stated that at no time had the blood-urea been higher than 50 mg. per 100 c.c.

Case 5. G. W., female, aged 45, was admitted to the Neurological Ward of the Middlesex Hospital on December 20, 1932, as she had lost consciousness in a bus on that date. She gave a history of severe periodic headaches commencing at the age of 30. These were referred to the frontal region and were throbbing in character. They were never preceded by any visual phenomena or accompanied by vomiting. In 1927, at the age of 39, she had her first attack of epilepsy, and since then she had had seven further attacks. The attack is always preceded by severe headache, frontal and occipital which comes on suddenly. If she is able to lie down quietly in the dark no fit usually occurs, otherwise after the headache has lasted for about five minutes she suddenly loses consciousness. She has been told that she goes stiff and then struggles in the attack. Occasionally she bites her tongue and is incontinent during the attack. The period of unconsciousness has lasted as long as two hours. After the attack severe headache persists for a day. Occasionally she has difficulty in expressing herself for a short time after the attack, but has never noticed any weakness in the limbs. No history of nycturia was obtained. Her general health between the attacks is good and she is able to carry on with her work, which is that of a midwife.

In 1928 she was admitted to the Middlesex Hospital under the care of Dr. C. E. Lakin, following her second attack of epilepsy. The blood-pressure during three weeks in hospital varied between 180/138 and 150/95. Blood-urea 40 mg. per 100 c.c. On readmission on December 20, 1932, she was conscious but complained of headache. The fundi were normal apart from a moderate degree of retinal arteriosclerosis. There were no abnormal signs in the central nervous system. There were signs of moderate hypertrophy of the left ventricle. Blood-pressure 230/140. W.R. negative in blood and cerebrospinal fluid. The pressure of the latter was 120 mm. of water. The urine contained a trace of albumin but no casts. Blood-urea 38, non-protein nitrogen 36 mg. per 100 c.c. Within twenty-four hours her blood-pressure fell to 200/120 and remained in that vicinity during her fortnight's stay in hospital.

This patient had her first fit at the age of 39. The occurrence of severe headache, recalling that of migraine, before each attack is of interest. Her blood-pressure on each of the two occasions on which she was admitted to hospital following an attack was considerably raised and fell rather more rapidly than could be accounted for by a day or two in bed. This suggests that the attacks of epilepsy were due to a sudden additional rise in blood-pressure. There was no evidence of nitrogen retention on either occasion.

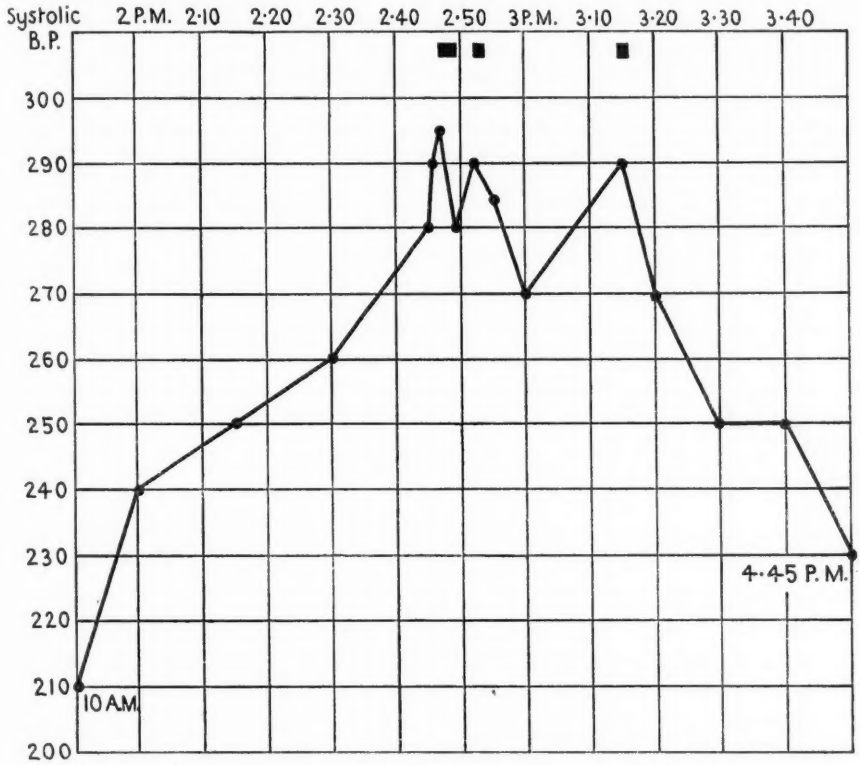
Not infrequently the convulsive attacks are preceded by signs of a gross cerebral lesion such as a hemiplegia, as seen in the following case which illustrates the part played by a rapid rise in blood-pressure.

Case 6. L. S., female, aged 44, was well until September 1931, when suddenly while she was doing her housework her right leg gave way and she dropped to the floor unconscious. Recovering consciousness a few hours later she could not speak nor move her right arm and leg. For a week she had periodic attacks of unconsciousness, but gradually improved and had partially regained speech and some power in the limbs by the end of two months. About this time she began to have fits, beginning on the right side of the body. These continued at intervals until her admission to the Hospital for Epilepsy and Paralysis, Maida Vale, in July 1932, under the care of Dr. F. Golla, to whom I am indebted for permission to observe and report the case.

On admission memory and attention were good. No speech defect was noted except following an attack. The pupils were normal in every respect. The fundi were normal except for a mild degree of retinal arteriosclerosis. There were signs of a mild right-sided hemiplegia without sensory loss. The left heart was moderately hypertrophied. Pulse 80 per minute. Blood-pressure 260/120. Urine contained no albumin. Blood W.R. negative. Cerebrospinal fluid-pressure 110 mm. of water. W.R. negative. Three cells per c.mm.: 0·03 per cent. protein.

During the patient's first four months in hospital she had typical attacks of Jacksonian epilepsy, beginning in the right arm and spreading down to the right leg and then across to the other side of the body with loss of consciousness. After these attacks a motor type of aphasia appeared and lasted about five minutes. Between July and November she had fourteen attacks. Treatment with Pacyl tablets (2 t.d.s.) was begun in the middle of October. The blood-pressure fell and the patient was free from attacks for a fortnight. On November 12 this treatment was stopped in order to make observations on the blood-pressure. It was recorded four-hourly.

It was observed that readings varied considerably between 210 and 250 systolic and 125 and 140 diastolic. An attack occurred on November 15 and was preceded by a rise in blood-pressure. A second attack occurred on November 20, 1932. The following observations were made on that day. A sphygmomanometer was retained on the arm from 2.30 until 3.45 p.m.



Case 6. Systolic blood-pressure readings November 20, 1932. Epileptiform attacks indicated by black squares.

10 a.m. Patient feeling well. B.P. 210/120. Pulse 80. *12 noon.* Rather anxious and uncomfortable. B.P. 230/120. *2 p.m.* Commencing tremor of right leg, feeling of numbness, and a 'funny feeling all over'. B.P. 240/125. *2.30 p.m.* More marked trembling of right leg and shoulder, twitching of both sides of the face, and an 'ice-cold sensation across the forehead'. B.P. 260/140. *2.45 p.m.* B.P. 280/145, no change. Pulse 90. *2·46 p.m.* Patient removed her false teeth and said a fit was coming on. B.P. 290/150. Pulse 110. *2.47 p.m.* Attack of Jacksonian epilepsy affecting right arm and leg, and left side of face. Patient unconscious for thirty seconds. No cyanosis or clenching of teeth. Consciousness returned quickly, followed by a period of temporary aphasia lasting forty-five seconds, patient trying to speak all the time. B.P. 295/150. Pulse 120. *2.49 p.m.* B.P. 280/130. Patient recovered her speech, and described a stiffness in left side of face, and a feeling 'as if she had washed and left the soap on that side'. She tried to rub this imaginary coating off her face. *2.52 p.m.*

Patient looked distressed, tried to speak but failed. B.P. 290/140. Pulse 120. No loss of consciousness, slight twitching right arm and leg, equal tremor both sides of her face. Patient described stiffness of left side of neck and face, with a feeling of heat over same area. *2.55 p.m.* B.P. 285/140. *3 p.m.* B.P. 270/140. Feeling normal. *3.15 p.m.* B.P. 290/140. Twitching both sides of face. No aphasia or loss of consciousness. *3.20 p.m.* B.P. 260/130. No further symptoms from now onwards. *3.45 p.m.* B.P. 240/120. *4.45 p.m.* B.P. 230/110.

On December 5 three attacks occurred. The blood-pressure rose to 300/150 just before the first attack.

Blood-urea and non-protein nitrogen estimated on several occasions never exceeded 40 mg. per 100 c.c. Serum-calcium 9·7 mg. per 100 c.c.

Despite continuous treatment with vasodilators, the blood-pressure has slowly tended to rise during the past five months and rarely can a figure below 280/140 be obtained. Several more fits have occurred, and on more than one occasion a figure of 300 systolic has been observed prior to an attack.

The observations made in this case illustrate the part played by a rapid additional rise in blood-pressure in precipitating an attack of epilepsy. Further, they point to the possibility of wide fluctuations in blood-pressure taking place in a few hours, which may account for a number of other symptoms met with in hypertensive patients, such as headaches and temporary focal signs.

A number of cases of epilepsy occurring for the first time in hypertensive patients over the age of forty have been observed within a few hours of their admission to hospital. The blood-pressure in such cases has always been much raised and has subsequently fallen more rapidly than could be accounted for by a few hours rest in bed. In this group of cases there has been no evidence of nitrogen retention. It is believed that in such patients a temporary further rise in blood-pressure has precipitated the attack. The adjective 'hypertensive' might be used in describing this form of epilepsy.

The importance attached to a rise in blood-pressure in precipitating both forms of hypertensive cerebral attack has already been indicated. There is, however, one group of cases in which a change in blood chemistry may be an additional and important factor, namely, cases of true uraemia complicated by convulsions. It must be pointed out, however, that many cases of uraemia die without having had a convulsion. It would be beyond the scope of this paper to discuss this aspect of uraemia further, but there is one change in the blood chemistry to which Bennett (2) has drawn attention in considering the question, namely the lowering of serum-calcium which may be a marked feature in certain cases of uraemia. The following case illustrates this point.

Case 7. Donald E., aged 11, was admitted to the Neurological Ward, Middlesex Hospital on April 2, 1933. His mother stated that he had never been robust and was subject to colds in the winter. In January 1933 he had chicken-pox, and since then it had been noticed that his face was slightly 'yellowish' and he did not seem so well as usual. On March 27 he vomited.

On March 31 and the following day he had four fits, these began on the left side. He was unconscious in one of these attacks for four hours. On admission he was conscious but drowsy. He complained of frontal headache. The skin of the face was yellowish. The breathing was deep. Both disks showed about three diopters of swelling, one small haemorrhage was noted above the right disk. Otherwise retinal changes were absent. The arteries were somewhat constricted. There was slight weakness of the left lower face, but otherwise no localizing signs in the central nervous system. The deep reflexes were brisk and the plantar responses were flexor. The cerebrospinal fluid was under increased pressure (no manometric readings taken). The heart was not enlarged; the heart-sounds were normal. Blood-pressure 132/78. The urine contained a large quantity of albumin. On palpation a large tumour was felt in the right side of the abdomen. It was firm in consistency and could be pushed forward by a hand placed posteriorly. The tumour was considered to be a polycystic kidney. The left kidney did not appear to be enlarged.

Blood-urea on admission 400, non-protein nitrogen 220 mg. per 100 c.c., and during the last twenty-four hours of life the figures were blood-urea 505, non-protein nitrogen 260 mg. per 100 c.c. The serum-calcium was estimated on one occasion, the figure was 4·8 mg. per 100 c.c.; phosphates 9·6 mg. per 100 c.c.

Muscular twitchings were observed and remained a prominent feature until his death one week later. During this time he had severe generalized epileptiform convulsions followed by coma. Hourly blood-pressure readings each day showed considerable variations in the figures. For example, on April 6 the highest figure recorded was 165/100 and the lowest 140/60. During that day he had a fit in the morning and another in the evening. The higher readings seemed to occur before and the lower soon after an attack. On the 7th the lowest blood-pressure reading was obtained at 6 a.m., namely 125/80 and the highest at 8.30 p.m., namely 170/110. No convulsions, however, occurred on this date, but the patient remained in a semi-comatose state.

The post-mortem examination (Bland Sutton Institute, No. 80, 1933) showed marked hydronephrosis on the right side with almost complete destruction of kidney substance, a small sclerotic left kidney, oedema of the brain with flattening of the convolutions, and a terminal broncho-pneumonia. Microscopically the brain showed dilatation of the perivascular spaces and thrombosis of a few small vessels; the left kidney showed advanced chronic glomerulo-tubular nephritis.

In this case of uraemia the serum-calcium was exceedingly low; this may in part have been due to the frequent vomiting. The lowering of the blood-calcium in all probability led to a heightened excitability of the whole nervous system. This was reflected in the muscular twitchings and it may well have been a factor in the production of the convulsions.

Minor Angiospastic Cerebral Symptoms

Apart from these severe attacks, certain other cerebral symptoms occur in hypertensive patients and are of particular interest as they point clearly to the existence of cerebral angiospasm. These consist of attacks in which temporary paresis, aphasia, paraesthesiae of cerebral origin, and disturbances of vision may be present. A feeling of numbness and tingling in the hand and around the mouth on the same side may be experienced, sometimes

accompanied by a motor type of aphasia if the vessel affected be in the left side of the brain. Such attacks may last for varying periods from a few minutes up to an hour or so. They may be followed by a permanent paresis. In such cases the vasoconstriction presumably is severe, and the resulting ischaemia produces permanent damage in a localized area. Accompanying these cerebral attacks there may be evidence of peripheral vasoconstriction in the limbs, either as a dead or tingling feeling in the hands or feet, or of pain in one lower limb of the type seen in intermittent claudication. Vision may be affected, independently of a retinitis, by spasm of a branch of the posterior cerebral artery which supplies the occipital pole. The amaurosis is usually temporary.

The following case in which cardiac infarction occurred illustrates these points.

Case 8. W. A., male, aged 31, was admitted to the Neurological Ward of the Middlesex Hospital on December 3, 1930. The patient was well until the spring of 1930 when he began to suffer from frontal headaches which became increasingly frequent and severe. He had never vomited. On one occasion in June he suddenly experienced a feeling of numbness and uselessness in the fingers of the right hand and at the same time speech became 'a little thick'. Two days later the right leg was similarly affected. These symptoms gradually passed off within two weeks. About the middle of November he caught a cold and remained in bed. On the fourth day he noticed that the uselessness and numbness in the right hand and leg had returned; subsequently the power improved again. Since that date he has had to rise once at night to micturate. He had never suffered from scarlet fever or recurrent tonsillitis.

He appeared apprehensive and pale. There were signs of moderate hypertrophy of the left ventricle. The radial artery was definitely thickened. Blood-pressure 210/140. There was no papilloedema and no evidence of a retinitis. There was well-marked retinal arteriosclerosis and the arteries were much constricted. Signs of a slight right-sided hemiplegia were present. Blood W.R. was negative. Cerebrospinal fluid pressure 140 mm. of water. No oedema of the ankles was noted. A trace of albumin was occasionally present in the urine, but no casts were seen. Blood-urea 35 mg. and non-protein nitrogen 36 mg. per 100 c.c

Frequent readings showed that there was some variation in the blood-pressure; the highest recorded being 238/140 and the lowest 160/110. A large number of septic teeth were extracted at seven different sittings. On February 2, 1931, he complained of a severe headache. Two days later signs of a slight left hemiplegia were found for the first time. These signs persisted until his discharge on February 14. On April 23, the patient wrote to me in reply to a letter inquiring as to the occurrence of any fresh symptoms: 'Actually I have had two attacks of weakness, the first being on March 21, causing a little difficulty in speech and slight weakness in the fingers of the right hand; this all passed off in an hour or two. The second attack was on March 29, and was exactly like the first, except that it was followed by bad headaches on the 30th and 31st. Both attacks came on suddenly. I was unable to lift a cup of tea with my right hand while it lasted.' During the night of August 2 he suddenly developed severe pain

referred to the left side of the chest accompanied by dyspnoea; the pain lasted intermittently for five days. Dr. W. E. Lock of Kettering noted 'rough systolic and diastolic murmurs all over the precordium, which had the characters of the murmurs in pericarditis'. Following this attack there was increased breathlessness on exertion. He was readmitted on October 31. The pallor of the face was now more marked. His weight in December 1930 was eight stone nine pounds. It was now eight stone. The size of the heart was approximately the same, but the apex beat was more diffuse. Blood-pressure varied between 200/132 and 170/130. The fundi showed no papilloedema and no haemorrhages; one small area of exudation was seen just below the left disk. The vessels still appeared markedly contracted. There were no fresh signs in the central nervous system. The urine was free from albumin on three occasions, but once contained 0·1 grm. per litre. The blood-urea was 43 mg. and non-protein nitrogen 31 mg. per 100 c.c. An electrocardiogram was taken by Dr. G. E. C. Ward who reported as follows: 'Regular sinus rhythm. Extreme inversion of *T*-wave in lead I. *T*-wave almost non-existent in lead II. Marked left ventricular predominance.' Dr. Lock wrote on December 15, 1932, that his condition showed little change and that he was still able to go about; his blood-pressure remained fairly steady in the region of 210/140.

Aetiology

The writer is in agreement with Volhard's views on the underlying changes in the brain in hypertensive states. He does not, however, believe that in an eclamptic convulsion there is always cerebral oedema. In a case recently seen through the kindness of Mr. L. C. Rivett, the cerebrospinal fluid pressure was normal; a progressive rise in blood-pressure was noted prior to convulsive seizures. Further observations on these points are necessary.

The factor common to both varieties of cerebral attacks is a raised blood-pressure. The actual precipitating cause seems to be a further rise in pressure. The proof of this is a matter of considerable difficulty as the rise may take place in the course of a few hours and it may be necessary to take frequent readings in order to establish the rise that precedes an attack.

In young persons the cerebral capillaries seem unable to adjust themselves to the rapid rise in pressure and cerebral oedema results. Angiospasm is probably not an essential factor in such cases but may co-exist. As soon as the cerebral circulation has adjusted itself to the new conditions prevailing, either spontaneously or as a result of treatment, the symptoms may subside. I have seen more than one case in which, although the cerebrospinal fluid pressure was much raised, e.g. 280 mm. of water or above, the patient at the time of the lumbar puncture was free from headache. Theoretically it is possible that, if as a result of cerebral oedema the intracranial tension is greatly increased, the blood-pressure may be forced to remain at a high figure in order to ensure an efficient circulation of blood to the brain as suggested by Blackfan. His observations were made on children. I have not been able to convince myself of this sequence of events in adults.

I have only once observed a cerebrospinal fluid pressure of 300 mm. of water in the more chronic stages of arterial hypertension. The following figures, recorded in a woman of 44, show that the diastolic blood-pressure was unaltered despite a marked lowering in the cerebrospinal fluid pressure.

Initial blood-pressure 198/132. Initial C.S.F. pressure 300 mm. of water.

10 c.c. C.S.F. withdrawn	B.P. 200/132	C.S.F. pressure 200
10 c.c. C.S.F. withdrawn	B.P. 192/134	C.S.F. pressure 170
10 c.c. C.S.F. withdrawn	B.P. 194/132	C.S.F. pressure 100

Similar results were obtained in several other cases. These findings would suggest that, at any rate in the more chronic cases, cerebral oedema plays a negligible role in the maintenance of the raised blood-pressure. However, during the initial acute stage when the cerebrospinal fluid pressure may be very high, it is possible that a compensatory further rise in blood-pressure may occur. If the intracranial pressure is very high, a 'pressure cone' may be formed through the forcing down of the tonsils of the cerebellum into the foramen magnum. In such a case, attempts to relieve the pressure by lumbar puncture may be quickly followed by death.

In middle-aged persons subject to chronic hypertension the sudden rise in pressure induces spasm of cerebral vessels with resulting ischaemia. The symptoms which follow probably depend, not only on the degree of spasm, but on the situation and number of vessels affected. If the process is a local one confined, for example, to a branch of the middle cerebral artery, Jacksonian convulsions may be produced. If, on the other hand, the angiospasm is widespread, then, in addition to generalized convulsions, coma results.

That there are other factors to be considered besides a rapid additional rise in blood-pressure is certain. Variations in blood-pressure are probably not uncommon in hypertensive patients, yet convulsions are comparatively rare. A second factor which seems to predispose a hypertensive patient to convulsions is the previous occurrence of a cerebral thrombosis by virtue of the local circulatory disturbance consequent upon such a lesion. A third factor, the importance of which it is difficult to estimate, is a change in the biochemistry of the blood. It is probable that this factor plays an important part in the convulsions of true uraemia. The experimental work of Forbes and Wolff and their collaborators has opened up a large field for speculation as to the effects of changes in the chemistry of the blood on the cerebral circulation.

It has been objected that an arteriosclerotic vessel is unlikely to undergo spasm as a result of changes in its walls. The type of case which is now under consideration is not the atherosclerotic with atheromatous plaques on the circle of Willis and in whom raised blood-pressure is quite often absent, but the victim of high blood-pressure and diffuse hyperplastic sclerosis (arteriocapillary fibrosis of Gull and Sutton) in whom the small arteries and arterioles in the body are widely affected. The changes, which have been fully described by Evans (4), consist initially of a hyperplastic thickening of the intima and hypertrophy of the media. Later, secondary changes take

place and there is fatty degeneration of the thickened intima of terminal arterioles which may lead to complete obliteration of the lumen. The middle coat also may undergo degenerative changes and fibrosis. Such changes, except in their later stages, should not materially interfere with the contractility of a vessel. Furthermore, since the lumen of the smaller vessels is narrowed through thickening of the intima it would require a smaller degree of spasm to produce ischaemic phenomena.

Prognosis

Recovery from both forms of hypertensive cerebral attack is the rule, provided there is no accompanying uraemia. If no steps are taken to treat the cerebral symptoms death may occur either as a result of medullary compression in the oedematous form or as a result of exhaustion following repeated convulsions in older persons. Treatment instituted at an early stage in either form usually hastens the termination of the attack. The ultimate prognosis will depend, in some degree, on the type of case. In a young adult the state of the kidney is the important factor. Leaving aside cases of acute nephritis, it may be said that during the acute phase of circulatory disturbance it may be impossible to decide whether the hypertension is primary or secondary to an old kidney lesion. The effect on the kidney will be much the same in either case, namely, a sudden reduction in its functioning power as a result of the acute disturbance of its normal circulation. A marked degree of albuminuria with hyaline casts and red cells as well as a reduced figure from the urea-clearance test are commonly found, whatever the cause of the hypertension. As long as the nitrogenous contents of the blood remain within normal limits then the immediate prognosis with regard to the attack is good. Subsequently it may be possible to determine the damage to the kidney which the sudden wave of raised blood-pressure has caused. In favourable cases of essential hypertension the albumin disappears from the urine, and tests for renal efficiency may show good figures. The blood-pressure usually remains, however, at a high level, and even though the kidney may recover well from such an attack it is only a question of a very few years at the most before death results from renal failure or a cerebral haemorrhage.

In older persons a fatal cerebral haemorrhage frequently occurs as a consequence of the periodic rises in blood-pressure, or an hypertensive cerebral attack may be followed by actual thrombosis resulting in a hemiplegia. The condition of the heart is more important than in younger patients in assessing the probable duration of life.

Treatment

As the essential factor in both forms of cerebral attack is believed to be a sudden additional rise in pressure, treatment should at once be directed

towards a reduction in pressure by the speediest methods. Good results have been obtained by a liberal venesection; the use of French's apparatus is advocated. In the form of hypertensive cerebral attack with signs of cerebral oedema, venesection will help towards a reduction in intracranial pressure. Further steps should, however, be taken. Intravenous injection of hypertonic salines will diminish headache. Lumbar puncture should also be carried out, firstly, with the purpose of determining the extent to which intracranial pressure has risen, and secondly as a therapeutic measure. Care should, however, be taken in cases where the pressure is high, as by the withdrawal of large amounts of cerebrospinal fluid a 'pressure conc' may be formed which may lead to a fatal termination. If the cerebrospinal fluid is under moderately increased pressure (approximately 200–250 mm. water) it is safe to remove 10 to 20 c.c. of fluid. If increased headache follows then no further lumbar puncture should be done.

In the form of attack without signs of cerebral oedema lumbar puncture and intravenous hypertonic salines are valueless. Venesection is the most important measure. An inhalation of amyl nitrite may bring to an end a series of convulsions; it should be followed by erythrol tetranitrate gr. $\frac{1}{2}$ three hourly until the blood-pressure begins to fall. The likelihood of further attacks may be lessened by the continuous use of vasodilators with a hypnotic such as luminal.

Summary

1. The cerebral symptoms formerly attributed to uraemia are not due to nitrogen retention but to disturbances of the cerebral circulation, as clearly shown by Volhard.

2. The work of Forbes and Wolff and others on the cerebral vessels clearly establishes the existence of a vasomotor nervous supply, not only to the pial vessels, but in all probability to the intracerebral branches as well.

3. The term 'hypertensive cerebral attack' is used to denote those cerebral symptoms which may occur as a result of a rapid rise in blood-pressure above a previously normal or raised level.

4. Two forms of attack are described. The type with signs of cerebral oedema is commonest below the age of 40. Severe headache is a constant feature. Concomitant signs, as in the eye grounds and urine, are usually present, and point to a generalized circulatory disturbance.

5. The type without signs of cerebral oedema occurs most frequently in middle-aged hypertensive subjects. Angiospasm is the important factor in producing the convulsions and coma. The adjective 'hypertensive' might be used to describe this form of epilepsy.

6. Certain minor cerebral angiospastic phenomena are described.

7. The etiological factors in the two forms of hypertensive cerebral attack are discussed, and of these it is concluded that a sudden rise in blood-

pressure is the most important. Subsidiary factors in certain cases are the occurrence of a previous cerebral thrombosis and an altered blood chemistry.

8. Indications for treatment are given.

I am indebted to Dr. A. B. Carter, House Physician to the Hospital for Epilepsy and Paralysis, Maida Vale, for his careful observations in Case 6, and to my medical colleagues on the staff of the Middlesex Hospital for the opportunities they have afforded me.

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THE ACTION OF ATROPINE IN COMPLETE HEART-BLOCK[1]

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With Plates 34 and 35

Complete block is an uncommon manifestation of heart disease, and in medical practice it is rightly regarded as a very rare condition. Among 5,000 consecutive patients submitted to electrocardiographic examination at the Royal Infirmary, Edinburgh, complete heart-block was demonstrated in only 31. Similarly White (26) found 79 instances of this disorder amongst 10,000 patients electrocardiographed, and Downie (5) 27 in 9,000 patients. Considering a total of 24,000 patients known or suspected to have heart disease, the incidence of complete block is therefore only 0·57 per cent.

Despite the rarity of complete heart-block, it has been my good fortune to have under my personal observation fourteen examples of this condition during the past five years. The opportunity has been taken to record the response of the blocked heart to various procedures.

In the present paper it is proposed to discuss the reaction of the blocked heart to atropine. In virtue of its power to inhibit vagus action, the accelerating effect of atropine on the normal heart is well known. In complete block it has long been a tradition that the paralysing influence of the drug is confined to the auricles, which therefore accelerate in the usual manner, but the ventricles isolated from the auricles continue to beat at their accustomed rate. So well established is this belief that it has formed the basis of a test for the differentiation of the extrinsic and intrinsic forms of bradycardia.

When François-Frank (9) in 1884 and Dehio (4) in 1892 put forward the suggestion that atropine might be used to distinguish the slow pulse of vagal origin from the other forms of bradycardia, hypothesis was ahead of knowledge, for it was only by the year 1899 that Wenckebach (25) and His (14) described block in man. Six years later Hay (13) was able to offer post-mortem evidence of a lesion situated in the auriculo-ventricular bundle in a patient in whom the diagnosis had been made during life. Even before the nature of the bradycardia of complete block or the Stokes-Adams syndrome were fully appreciated, the therapeutic use of atropine was occasionally advised. One of the earliest records is that reported by

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Kinkead (16) in 1898, in which it is recounted that the heart-rate in a man under his personal observation declined to 6 per minute and continued to beat rhythmically at this slow rate for probably six or seven hours. After a hypodermic dose of atropine the rate rose to 72 per minute. In the light of modern knowledge this case may probably be interpreted as an example of intermittent complete heart-block with numerous Stokes-Adams attacks. The restoration of conduction would account for the rise in ventricular rate. It is questionable if the small dose of atropine used (1/100 gr.) was responsible either for an increase in rate or for release from the block. After 1905 many undoubted instances of complete heart-block were reported from all parts of the world. In some of these the use of atropine as a diagnostic test or as a therapeutic agent is described; but, more often than not, precise data are lacking, and in many the dose used is either not stated or is too small in amount to be regarded as really effective. It is unnecessary to review these cases in detail, as the universal opinion, culled from a consideration of the available data, is that atropine is not only valueless as a therapeutic agent in complete block, but has no appreciable action on the rate of the ventricles.

As a result of experimental work on animals, various authors came to the conclusion that atropine was without appreciable effect on the ventricles in the completely blocked heart. Erlanger (7, 8), the first to study the physiology of experimental block, pointed out as early as 1905, that whereas atropine accelerated the auricles it was without influence on the ventricles isolated by transection of the bundle of His. In 1913 van Egmond (6), working on the cat's heart, came to the conclusion that atropine had no appreciable effect on the ventricles in the presence of complete block. Cullis and Tribe (2) came to similar conclusions, and reasoned that the ventricles did not receive vagal fibres. For the most part these were all acute experiments and not strictly comparable to the chronic vascular degenerative lesion commonly found in man. It is only natural to suppose that the disturbance produced by cutting or clamping the bundle with the associated bruising and local haemorrhage, must act to some extent as a local irritant and thereby induce a somewhat artificial rate of stimulus production in the specialized tissues immediately below the lesion. The results obtained in the laboratory, therefore, suggest that atropine has little or no effect on the ventricular rate in the blocked heart.

In man the general view is that atropine is as ineffective in accelerating the ventricular rate as it is in the blocked heart of the animal. Vacquez (22) concluded from the study of a group of cases of bradycardia that atropine had little or no influence on the pulse-rate in that form due to intracardiac lesions. On the other hand, Pétzétakis (19) found that certain cases of slow pulse of non-myocardial origin were uninfluenced by atropine, and Frédéricq (10) concluded that reliance should not be placed on the atropine test as a means of distinguishing between the different forms of slow heart action. In support of this view it is of interest to refer to the recent work

of Kauf (15), who found that, in contrast to the untrained individual, the heart of trained athletes did not accelerate after a dose of 1 mg. of atropine sulphate.

Clinicians have generally held to the view that the slow idio-ventricular rate of complete heart-block was quite uninfluenced by atropine. Ritchie (20) in his Gibson Memorial Lecture expressed the current opinion when he said 'The intravenous administration of atropine is the most prompt and effective measure in warding off the risks which attend a severe grade of partial block. Although all the chambers of the normal heart are accelerated by atropine, the drug has no direct action on the ventricles. This fact is well demonstrated by a study of the effects of atropine in complete auriculo-ventricular dissociation. Here atropine does not increase the ventricular rate, although the auricles are accelerated.'

On reviewing the case reports in the literature it would appear that not infrequently conclusions have been drawn from the effects obtained by the administration of too small a dose of atropine. Lewis and his colleagues (18) have found that in dogs of about 10 kilos, 0·1 mg. of atropine sulphate had a very decided effect in weakening the inhibitory terminations of the vagus, but that this dose must be increased to 0·2 or 0·4 mg. before the effects of even weak peripheral stimulation are abolished. To render strong vagal stimulation ineffective, the dose had to be increased to 0·05 to 0·1 mg. per kilo of body weight. From similar observations on man they came to the conclusion that 1/50 gr. of atropine sulphate, given by intravenous injection, is sufficient to produce very decided effects on the heart, nearly, but not quite, paralysing the vagi. To produce complete paralysis a dose of 1/20 to 1/10 gr. is required in man. Very few cases of complete heart-block have been tested with doses of atropine sufficient to produce complete or almost complete paralysis. Before it can be concluded that the idio-ventricular rate is irresponsive to atropine, it is desirable, in the light of recent knowledge, to employ a dose of at least 1/50 gr. intravenously. The dose used in the series of cases reported here was a uniform one of 1/30 gr. intravenously. This amount was found to be sufficient to produce quite decided effects on the rate of the ventricles, and as the same dose and a similar experimental technique were employed through the series, the results obtained are comparable.

Experimental Methods

Of the fourteen patients under observation the response of the heart to 1/30 gr. of atropine sulphate was tested in ten. Others receiving a smaller dose, and one patient in an advanced stage of congestive heart failure at the time of the test, are excluded from the present series. All had been under observation for varying periods of time, and repeated electrocardiograms had conclusively demonstrated the presence of complete dissociation in each. As the results obtained are contrary to prevailing opinion, it seems desirable

to record the experimental technique in detail. The patients were brought from their beds in a wheeled chair to the electrocardiograph department and allowed to rest on the examination couch for an hour or more until the pulse-rate and blood-pressure reached a constant level. All the subjects were investigated in a similar manner, and each was already well acquainted with the surroundings and workers in the laboratory. The room temperature was comfortable, the patients were shielded from draughts, and strangers were excluded. Each patient lay in a position of maximum ease with the hands and left foot immersed in the warm saline solution of the non-polarizable electrodes. All were under constant observation throughout the experiment.

Three electrocardiograms were recorded at intervals of five minutes or thereabout, before the dose of atropine was administered, the last one being taken immediately before the needle-point was inserted into a convenient vein at the bend of the elbow. The dose employed was the same for each patient, viz. 1/30 gr. of atropine sulphate dissolved in 1·0 c.c. of sterile normal saline and administered intravenously. In order to avoid, as far as possible, any reflex acceleration of the heart which might result from the pain of the needle prick, a particularly sharp needle of fine bore was used. A minute was allowed to elapse after the needle had entered the vein before the solution of atropine was injected. In this way the possibility of the registration of a transient acceleration due to pain or excitement was in a large measure avoided.

Given by the intravenous route, a dose of atropine acts with great rapidity, and the maximum acceleration of the heart-beat is reached, as a rule, within two or three minutes from the time of the drug's injection. A succession of slow running plates was therefore exposed at short intervals. The first of these was photographed immediately the injection was completed. At intervals of half a minute, or a minute, succeeding records were made, and after the first three exposures further electrocardiograms were registered every two minutes until one hour had elapsed from the time of injection. In a number of cases simultaneous blood-pressure readings were made, using the auscultatory method and the Baumanometer apparatus. Notes were made of the patient's reaction to the drug, e.g., dryness of the mouth, paralysis of the iris, or general restlessness. Incidentally, a control injection of normal saline alone was made in one or two cases, using a similar technique throughout.

Thirty or more electrocardiograms were recorded during the experimental period. Each of these was subsequently analysed, often in duplicate, as regards auricular and ventricular rates. The time-marker recorded accurately in fifths and twenty-fifths of a second, and it was therefore possible to measure the deflections to 0·01 second with the aid of a hand lens. A comparator was not found to be necessary.

The Response to Atropine

The effect of the dose of 1/30 gr. of atropine sulphate intravenously on the auricular and ventricular rates is shown in the following table (No. 1). In spite of the very marked acceleration observed in certain cases, in not one instance was the degree of heart-block reduced. The dissociation in every instance remained complete.

TABLE I

To Show the Accelerating Effect of Atropine on the Auricular and Ventricular Rates in 10 Cases of Complete Dissociation.

Case No. and initials.	Age in years.	Height in in.	Weight in lb.	Auricular rate per min.		Gain in rate. Auricles.	Percentage gain in rate. Auricles.	Ventricular rate per min.		Gain in rate. Ventricles.	Percentage gain in rate. Ventricles.
				Before.	Max. rate after.			Before.	Max. rate after.		
1 Mrs. T.	55	65	131	75·3	101·6	26·3	34·7	22·2	23·4	1·2	5·4
3 D. C.	64	67	161	72·0	127·4	55·4	77·0	42·8	62·3	19·5	45·6
4 W. T.	65	71	178	63·1	80·1	27·0	42·3	23·6	26·4	2·8	11·9
5 A. H.	64	64·5	119	72·5	92·3	19·8	27·3	31·0	39·8	8·8	28·4
6 J. W.	48	68	151	57·7	77·0	19·3	33·5	28·5	30·3	1·8	6·3
8 J. B.	47	65	137	Auricular fibrillation present				30·7	41·0	10·3	33·5
10 Mrs. C.	84	60	?	"	"		"	26·7	31·3	4·6	17·2
12 J. D.	50	63	114	91·3	135·0	43·7	48·0	49·3	96·3	47·0	95·9
13 Mrs. H.	57	64	175	77·3	100·5	23·2	30·0	42·6	76·4	33·8	79·4
14 Mrs. D.	63	61·5	144	64·6	87·0	22·4	34·7	29·1	32·8	3·7	11·3

An increase in ventricular rate after the dose of atropine occurred in each individual examined—the figures derived from those patients who each received a 1/30 gr. intravenously being presented in the table. The maximum gain in ventricular rate occurred in Case 12. The patient's ventricular rate increased from 49·3 to 96·3, a range of 47·0 representing a gain of 95·9 per cent. The minimum range was that recorded in Case 1. Before injection the ventricular rate was 22·2, some minutes after the dose it was 23·4, a gain of 1·2 beats per minute, a 5·4 per cent. increase over the resting value. The table shows that the gain in auricular rate was, on the whole, less variable than the ventricular, the maximum being 55·4 per cent. in Case 3, and the minimum 19·3 per cent. in Case 6. These figures clearly cast a doubt upon the statement frequently made that atropine has no effect, or only a trifling one upon the rate of the ventricles in complete heart-block. It further emphasizes how valueless the atropine test is as a means of distinguishing bradycardia due to complete heart-block from other causes. As the figures show, even in the presence of complete dissociation, the ventricles may accelerate by as much as 95 or 80 per cent.

To establish the view that atropine when injected intravenously is directly responsible for the acceleration observed, it would be desirable to show that the rate after the drug's administration not merely exceeded the ventricular frequency immediately before its use but was, in fact, greater than the maximum spontaneous rate observed under similar conditions of bodily rest.

In certain experiments with normal saline, in place of atropine, a gradual decline in ventricular rate was observed. By recording electrocardiograms after an hour's rest on a couch at intervals of a few days, it has been possible to show that, despite the presence of complete heart-block, the ventricular rate varies from day to day by a few beats per minute in the same patient. The ventricular rate is not a fixed quantity, but exhibits a minor degree of fluctuation, reflecting in some measure the changes in auricular rate. By these simple methods it has therefore been possible to assess the natural spontaneous range in ventricular and auricular rates under uniform conditions of bodily rest in the case of each patient studied.

TABLE II

To Show that the Rate after Atropine Exceeded the Natural Maximum Rate under Similar Conditions of Bodily Rest in 8 of 10 Individuals.

Case No.	Maximum rates after 1 hour's rest. Ventricles.	Maximum rates after atropine from Table I. Ventricles.	Ventricular gain over maximum resting rate.
1 Mrs. T.	29·2	23·4	—
3 D. C.	42·8	62·3	19·5
4 W. T.	23·6	26·4	2·8
5 A. H.	36·0	39·8	3·8
6 J. W.	28·5	30·3	1·8
8 J. B.	33·0	41·0	8·0
10 Mrs. C.	26·8	31·3	4·5
12 J. D.	55·2	96·3	41·1
13 Mrs. H.	42·6	76·4	33·8
14 Mrs. D.	? 30·0	32·8	? 2·8

In order to present adequate proof that the acceleration observed after the injection of atropine was due to the drug, it is necessary to establish the fact that the rate so recorded was greater than the natural spontaneous maximum rate recorded under similar conditions of rest for each individual. About half a dozen determinations of the auricular and ventricular rates during bodily rest were made at intervals of a few days for each patient, and the results are incorporated in Table II. The figures demonstrate that amongst the individuals the maximum rate after 1/30 gr. atropine was definitely greater than that observed to occur under similar conditions of bodily rest in eight subjects. In one patient (Case 1) the acceleration recorded after atropine was less than that which might occur spontaneously. In another subject (Case 14) the upper limit of the spontaneous variations in resting rate could not be determined with sufficient accuracy to allow of strict comparison. In this patient the block, though complete, was complicated by an irregularity of the idio-ventricular rhythm—with the result that distinct but transient variations in rate made the upper limit of the spontaneous variations difficult to determine for more than relatively short periods of time. The average resting rate in this patient was, however, in the neighbourhood of 30 per minute. Considering the group as a whole it may be said that the intravenous injection of 1/30 gr. of atropine sulphate

increased the idio-ventricular rate; and applying the more stringent test associated with the spontaneous ventricular range, it may be said that atropine induced an increased ventricular frequency greater than the maximum natural rate in eight out of ten instances.

The Ventricular Range after Atropine

It has been shown above that in the presence of complete heart-block, atropine increases the idio-ventricular rate. The table shows that the gain

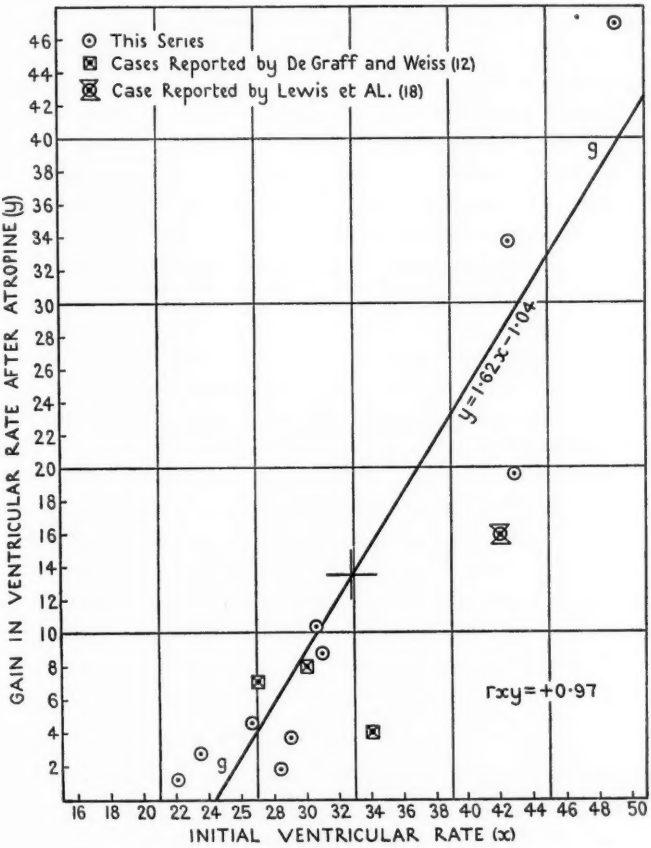
This Series
Cases Reported by De Graff and Weiss (12)
Case Reported by Lewis et AL. (18)
y = 1·62x - 1·04
rxy = +0·97
GAIN IN VENTRICULAR RATE AFTER ATROPINE (y)
INITIAL VENTRICULAR RATE (x)

CHART 1.

in rate varies considerably in different individuals. The state of affairs is best demonstrated by plotting the range (i.e. the gain in ventricular rate) against the rate observed immediately before the injection. This has been done in the accompanying Chart (No. 1) in which x = the initial ventricular rate and y = the observed ventricular range after atropine. These values are plotted one against the other for each individual.

By this means it is possible to demonstrate effectively that there is a

measure of agreement between the acceleration produced by atropine and the rate existing immediately before the injection. The greater the initial ventricular rate, the greater is the degree of acceleration produced, and vice versa. Mathematical analysis established a high and striking degree of correlation for this series of cases—the coefficient being $+0{\cdot}97$. The probability is, however, that the law expressing the relation between the initial rate and the degree of acceleration after atropine, is not best represented by a straight-line formula. As the plottings are too scanty in number to determine the optimum expression, the regression line g–g has been entered on the chart. This line represents the theoretical gain in rate (y) for a given initial rate (x), and has been drawn to the equation $y = 1{\cdot}62x - 1{\cdot}04$. It is evident from the graph that the regression line g–g cuts the base line at a value approximately 24. Theoretically this would imply that for the initial rates below 24 per minute, the response to atropine would be a minus quantity—in other words, slowing of the heart would follow the drug's administration. On the other hand, for initial rates above 24, acceleration might be anticipated as indicated by the lie of the line g–g. There is no particular reason to believe that such a peculiar state of affairs does exist in fact. In practice a negative response was never encountered, and the obvious explanation is that the relation between rate and range after atropine is probably best expressed by a curve—perhaps logarithmic—rather than by a straight-line formula. The points, as plotted in the chart, are rather few in number to yield precise information regarding the law expressing the relation between the rate before and the maximum rate after 1/30 gr. of atropine. That the initial rate and the associated increment may vary in a logarithmic way can be demonstrated by plotting the logarithm of the initial rate against the logarithm of the increment observed at that rate. When this is done (Chart 2) the points fall along an almost perfectly straight line. If this relationship be true throughout the whole of the available range, then the law expressing the reaction of the ventricles to atropine might be represented by some such equation as $\log Y = \log K + N \log X$, where X = the initial rate and Y = the increment at that rate. The observations recorded in these patients are not, however, in themselves sufficient in numbers to allow of the exact determination of the best expression of the relation between initial rate and effect produced.

Mention has already been made that at a theoretical rate of approximately 24 per minute a change occurs in the nature of the response to atropine. It has been shown that at initial rates in excess of 24 quickening occurs after the administration of the drug, and that the degree of acceleration bears a relation to the pre-existing rate. Theoretically at initial rates less than 24 the drug ought to produce slowing—if the law be represented by a simple straight-line formula. In this connexion it is not without interest to refer to the response of the blocked heart to digitalis (II). In a number of cases it has been found that, despite the presence of complete block, full therapeutic doses of digitalis induce a certain amount of slowing if the

initial rate be in excess of 24 per minute. Digitalis administered to one patient with an initial rate less than 24 per minute induced transient acceleration of the idio-ventricular rate. Apparently atropine and digitalis, at least in the presence of complete block, act through a similar mechanism but in a reverse manner in so far as these drugs influence the rate of stimulus production.

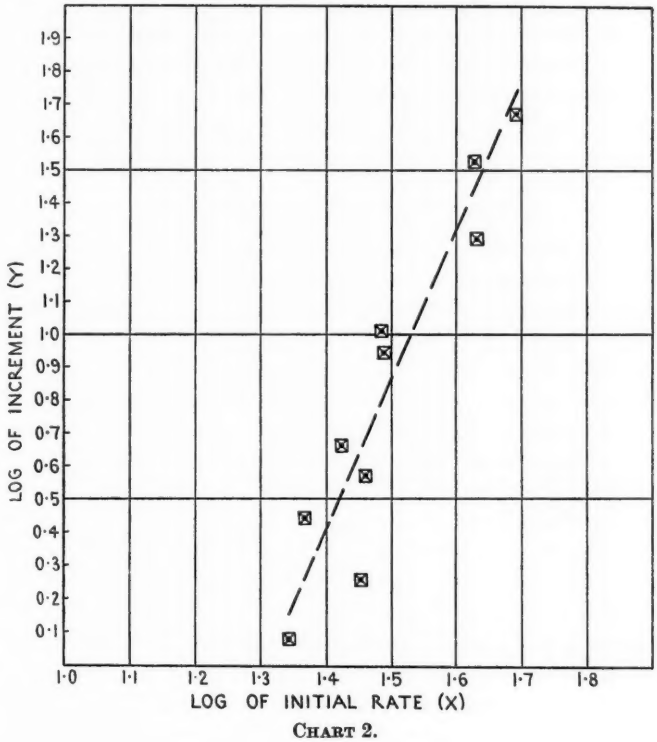

CHART 2.

The Auricular Range after Atropine

It has been shown above that the ventricular response to atropine depends chiefly upon the rate at the time of injection. This observation is rendered the more surprising when the data concerning the auricular response in the blocked heart are analysed. The facts are recorded in Table No. 1, in which the auricular rates immediately before, and the maximum after, are presented. In contrast to the ventricular response, it is not possible to demonstrate a relation between the initial auricular rate and the associated increment. In two patients (Cases 8 and 10) auricular fibrillation accompanied the block, and hence comparable figures are not available. The maximum auricular range in eight cases of complete dissociation was 55·4 in Case 3 (an increase of 77·0 per cent.), and the minimum gain was 19·3 beats

per minute (an increase of 35·5 per cent.). The facts at our disposal indicate that while ventricular acceleration bears a close relation to the initial rate, this rule does not apply to the auricular response to atropine.

The lack of agreement between auricular range and pre-existing rate finds support in the observations of Crawford (3). From a study of a large series of normal individuals and patients suffering from various types of heart disease, Crawford found that the rate after atropine could not be foretold from the rate existing before the drug was given. This observation would support the natural conclusion that the auricles in complete heart-block respond to atropine very much after the same manner as they do when the normal pacemaker is in full control of the heart beat. On the other hand, it must remain an open question as to the nature and cause of the peculiar ventricular response.

Crawford (3), in his study of the response of the heart beating in normal rhythm, found that the reaction to atropine was influenced by the age of the individual tested, being maximum between the ages of 20 and 30. After 50 years of age there was a distinct and progressive decline in the degree of acceleration induced, despite a dose proportionate to the body weight. Similarly it was found that, as compared with the healthy individual, the subjects of chronic heart disease, with the exception of those suffering from auricular fibrillation, yielded a diminished response to the drug. As the patients in this series of cases ranged from 47 to 84 years of age, and as their weight also varied considerably, it is all the more surprising that the degree of correlation between the initial ventricular rate and the acceleration produced should be so perfect. Furthermore, it has long been known that in the presence of valvular heart disease (more particularly when aortic regurgitation is the predominant lesion) the response to atropine is considerably diminished (3). Nevertheless, the degree of ventricular acceleration was apparently but little modified in the two patients (Cases 3 and 8) included in this series, both of whom suffered from a distinct regurgitant leak at the aortic orifice.

From what has been written it is not surprising to find that there is no obvious relationship between the auricular and ventricular ranges after atropinization. The first varies in an irregular manner from individual to individual, even in health, and evidently quite as much in the presence of complete block. The ventricular range, on the other hand, is largely determined by the pre-existing rate. After atropine the upper and lower chambers of the heart run their own individual course; the one is not apparently complementary to the other.

Smith, Burwell, and de Vite (22) found in normal men, after an intravenous dose of atropine, that the cardiac acceleration was accompanied by a diminution in the output of blood per beat with but little alteration in the volume of blood-flow per minute. In all probability a similar state of affairs holds good in the blocked heart under atropine. Actually the rates of the auricles and ventricles appear to be independent, and in the absence

of peripheral dilatation, it seems justifiable to conclude that though the ventricular rate is increased by atropine, the stroke volume is in all probability reduced. It is equally possible that by its action on the vagus atropine disorganizes the Bainbridge reflex, with the result that the auricular rate becomes virtually independent of the venous return.

Crawford (3) and Smith, Burwell, and de Vite (22) detected no constant change in blood-pressure readings after atropinization either in health or in the presence of diseased hearts. The lack of variation in the blood-pressure level after atropine administration to these cases of heart-block serves to illustrate the remarkable adjustability of the circulatory mechanism in spite of the presence of complete dissociation.

The Course of the Reaction to Atropine

The course of the response, as it affects the chambers of the heart, is best depicted by plotting the auricular and ventricular rates against time elapsing after the injection. Two examples, selected from ten experiments, are shown in the accompanying charts (No. 3 and 4). In Case 4 (Chart 3) the initial auricular and ventricular rates were respectively 63·1 and 23·6 per minute. At the height of the reaction the auricles had gained 27·0 beats and the ventricles 2·8. On the other hand, in Case 13 (Chart 4), the initial rates were 77·3 for the auricles and 42·6 for the ventricles. Atropinization induced rates of 100·5 and 76·4 respectively. At a relatively high pre-existing rate a large increment is recorded. Electrocardiograms, taken immediately before the injection and at the height of the reaction in these two patients are recorded in Figs. 1 and 2.

Very similar curves of atropine effect were recorded in the other cases. In some, the maximum effect was registered within the first minute; in others, three to five minutes after the injection. In general, the maximum acceleration occurred synchronously in auricles and ventricles, and by the end of an hour the ventricles had returned to their original rate, the auricles being a few beats quicker than in the control records. That the response should be of such relatively short duration is somewhat surprising in view of the fact that dilatation of the pupil and some dryness of the mouth often tended to persist after the cardiac effects had subsided. Some degree of mydriasis was generally obvious twelve to twenty-four hours after the test. There is no very satisfactory explanation why recovery should be more gradual in the termination of the parasympathetic fibres of the third nerve than in the tenth. No toxic symptoms of any significance were encountered in these patients after the intravenous administration of 1/30 gr., with the single exception of Case 10. This patient was an arteriosclerotic subject, 84 years of age. About one hour after the injection she became confused, excited, and developed an erythematous flush affecting the skin of the face, neck, and upper part of the chest. By the following day she had completely recovered.

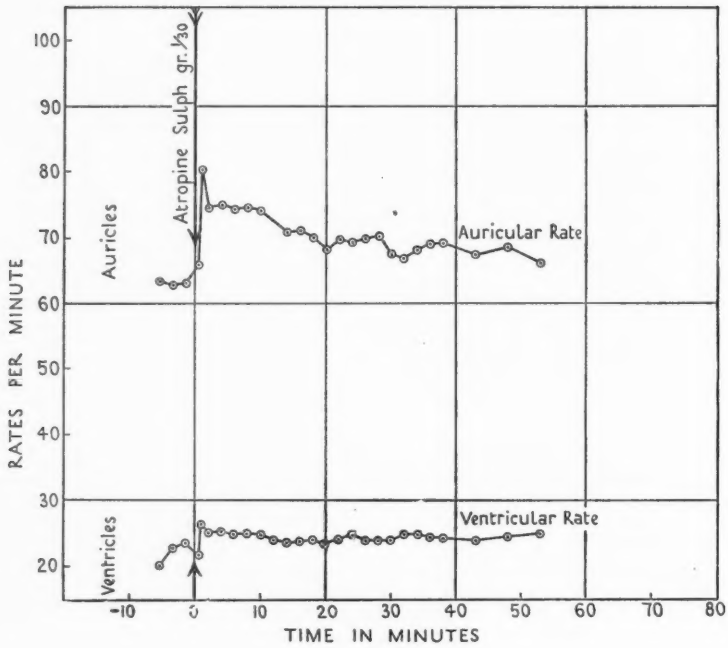

CHART 3.

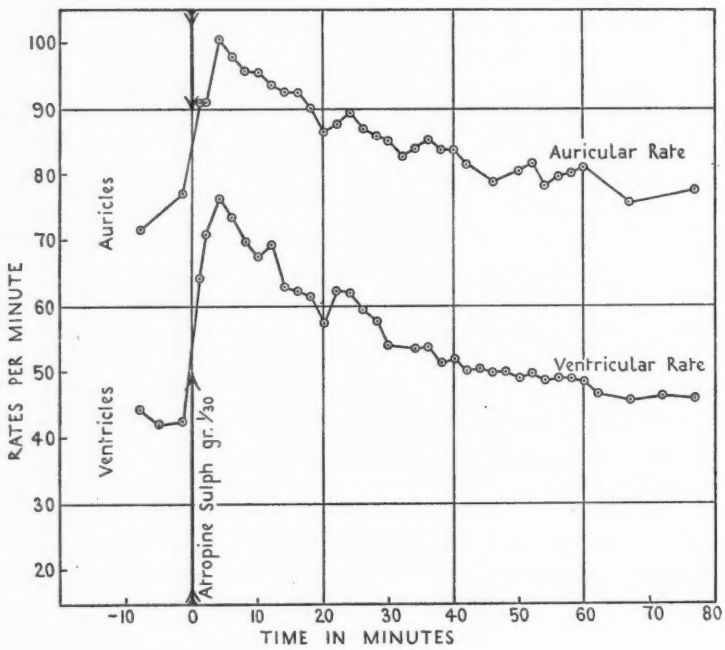

CHART 4.

No striking changes occurred in the form of the electrocardiograms after atropine. Extra-systoles were infrequent, and when they did occur they have not been included in the calculation of the heart rates. Coupled rhythm of short duration was only observed once in one individual after atropinization. In no instance did the degree of block decrease. In certain cases the *T*-waves, during the higher rates of beating, appeared to increase slightly in amplitude. The *P*-waves were occasionally larger after the injection than in the control records, or towards the end of the experiment. Similar changes have been observed to occur in health after atropine administration.

Discussion

Very few cases of complete heart-block in man have been tested with doses of atropine sufficient to produce complete or almost complete vagal paralysis. Lewis (18) briefly mentions one case complicated by auricular fibrillation. This man received 1/10 gr. of atropine sulphate intravenously, and fifteen days later 1/20 gr. A prompt rise in ventricular rate was observed on both occasions. From the chart in this author's publication, it would appear that the ventricular rate rose from 42 to 58—the increment being about equal on the two occasions. The response in this single individual, which is in keeping with the reaction observed throughout the series of cases at present under consideration, has been entered in Chart 1. Similarly, de Graff and Weiss (12) have tested the response of four cases of complete heart-block with larger doses of atropine than those generally employed. They injected hypodermically 5·0 mg. in three cases and 3·5 mg. in another, and found 'a slight but distinct increase in the ventricular rate'. The results obtained after the use of 5·0 mg. have also been entered in Chart 1. Ritchie (21) in 1927 tested one of the cases included in the present series (Case 3) with 1/50 gr. atropine subcutaneously. Before the injection the auricular rate was 70 and the ventricular 38. One hour later the respective rates were 92 and 42.

From these considerations it would appear that with sufficient dosage and a careful technique definite ventricular quickening is induced by atropine, despite the presence of complete heart-block. The variability of the degree of auricular acceleration leads to the conclusion that the response of the auricles may be regarded as an expression of the degree of vagal tone existing at the time of the injection. A large reaction to atropine predicates a pacemaker of high rhythmicity effectively held in check by a vagus centre of adequate tone. A small auricular response from an average rate may be taken to represent a less active nerve centre, probably coupled with a reduced rhythmicity of the sino-auricular node.

Considering the nature of the ventricular response, it is obvious that some other mechanism related to the initial idio-ventricular rate must hold sway. This at once suggests that the natural rhythmicity of the centre of stimulus

production determines the ventricular response. Lewis (17) has shown that the natural frequency of the *s-a* node is greater than the frequency of the *a-v* node, and there is every reason to suppose that the spontaneous rhythmicity declines as the conducting tract is followed to its termination in the Purkinje tissue. In other words, when the lesion transects the upper part of the *a-v* node, then the site of effective stimulus production is likely to be relatively high in the conducting tract. A centre of stimulus production immediately below a lesion in the *a-v* node is likely to have a greater spontaneous rhythmicity than one at the level of the bifurcation of the main bundle. It is known that the *a-v* node, bundle of His, and its branches receive vagal fibres (24). When the vagus is paralysed by atropine the response of the ventricles must be limited by the natural frequency of the controlling centre of impulse production. In other words, the higher the centre, the greater the possible response. It is therefore suggested that the peculiar nature of the ventricular response to atropine is primarily determined by the site of the lesion producing the block, an idio-ventricular centre situated in the upper regions of the conducting tract of relatively high natural rhythmicity, yielding a maximum response to atropine, and vice versa.

As a converse of this it would follow that vagal stimulation in complete heart-block is more likely to be effective in those instances in which the idio-ventricular rate is relatively high. As will be shown later, there are some grounds for believing that this supposition is correct.

Summary and Conclusions

The response of ten individuals suffering from complete heart-block has been tested by the intravenous administration of 1/30 gr. of atropine sulphate. Repeated electrocardiograms, taken at intervals before and after the injection, demonstrated that in every case studied, this drug produced an acceleration of the ventricular rate.

The prevailing view, constantly repeated in the literature, that atropine has little or no effect on the frequency of the ventricles is incorrect, and requires modification in the light of the peculiar character of the acceleration. The dose of atropine was sufficient to produce almost complete paralysis of the vagus. The maximum increase in ventricular rate was 47 beats per minute, representing a gain of almost 96 per cent. over the initial rate. The minimum acceleration was 1·2 beats per minute, giving a percentage increase of 5·4. In only one case was the gain after atropine within the maximum range recorded under similar resting conditions.

The initial ventricular rate is the important factor in determining the amount of acceleration for a given dose of atropine, the higher the resting rate the greater the response to atropine. At low initial rates atropine produces but little acceleration. The coefficient of correlation between the

rate before atropine, and the amount of ventricular acceleration produced by it is +0·97—a very significant relationship.

The law expressing the degree of acceleration for a given initial ventricular rate has been represented by a straight-line formula. Actually, this is probably not the best expression. It would appear from the available data, that a logarithmic curve might be the best expression, but the facts are too scanty to allow of its exact determination.

The use of atropine as a means of distinguishing the bradycardia of complete heart-block from other causes is therefore unreliable. Further work requires to be done on this subject with the object of determining the precise nature of the response to atropine in those cases of slow heart action in which complete heart-block is not present.

To obtain a decided effect on the ventricular rate, it is necessary to use an amount of atropine approaching the full paralysing dose; 1/30 gr. of atropine given intravenously in 1 c.c. of normal saline was found to be sufficient.

In contrast to the ventricular response, the auricular acceleration does not appear to bear any relation to the initial auricular rate. Further, the auricular range after atropine does not bear any relation to the ventricular. The amount of auricular acceleration varies irregularly from individual to individual. The auricular response probably reflects no more than the degree of vagal tone existing at the moment of injection.

The nature of the ventricular response suggests that the amount of acceleration is determined by the inherent rhymicity of the specialized tissue at the centre of impulse production. It is suggested that when the lesion producing the block is situated in the uppermost part of the conducting tract, a greater response will occur after atropinization than when the centre of impulse production lies at a lower level in the specialized tissues.

As a converse of this it may be suggested that vagal stimulation is more likely to be effective in slowing the idio-ventricular rate when the centre of impulse production lies high in the conducting tract.

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DESCRIPTION OF CHARTS

CHART 1. To show the relation existing between the rate of the ventricles before, and the maximum rate attained after an intravenous injection of 1/30 gr. atropine in ten cases of complete heart-block. The line g–g drawn to the equation $y = 1{\cdot}62 \times -1{\cdot}04$ represents the gain in rate (y) for a given initial rate (x). The coefficient of correlation (% xy) = $+0{\cdot}97$. The results reported by de Graff and Weiss and by Lewis have also been inserted in the chart.

CHART 2. To show that, the initial rate and the associated increment after atropine probably vary in a logarithmic way. By plotting the log of the initial rate against the log of the increment it is found that the points fall along an almost perfectly straight line.

CHART 3. To show the course of the reaction in auricles and ventricles in Case 4. At an initial ventricle rate of 23·6 the ventricles only increased in rate by 2·8 beats per minute. Contrast the reaction (in Chart 4) at an initial rate of 42·6.

CHART 4. To show the response of the auricles and ventricles in Case 13. At the relatively high rate of 42·6 beats per minute, the ventricles accelerate after atropine to 76·4, a gain of 33·8. These two cases (nos. 4 and 13) are selected to show the difference in the height and course of the reaction—a difference which depends largely on the rate existing before the administration of the drug.

	Rates. Auricles	Ventricles
5½ minutes before atropine	63·4	20·1
3½ „ „ „	62·9	22·9
1½ „ „ „	63·1	23·6
½ minute after atropine	65·7	21·8
1 „ „ „	80·1	26·4
2 „ „ „	74·4	25·2

Fig. 1. Case 4. To show the electrocardiograms recorded before the injection and those at the height of the reaction in Case 4. In this and the succeeding figure the lead number is marked in the upper left-hand corner and the standardization of the fibre is 1cm. = 1 millivolt

	Rates.	
	Auricles	Ventricles
8 minutes before atropine	71·8	44·4
5 „ „ „	–	42·2
1½ „ „ „	77·3	42·6
4 minutes after atropine	100·5	76·4
6 „ „ „	98·1	73·6
8 „ „ „	95·9	69·8

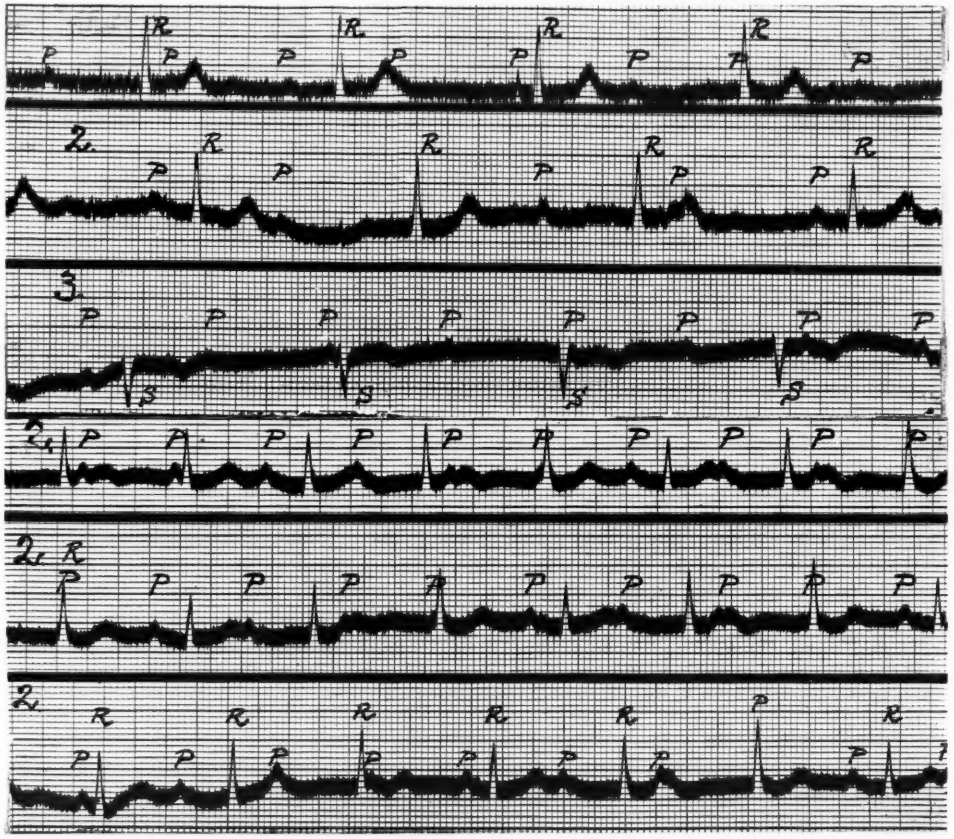

FIG. 2. Case 13. To show the electrocardiograms recorded before the injection and at the height of the atropine reaction in Case 13. Although the ventricles beat at a rate of 76·4 per minute 4 minutes after the administration of the drug, complete heart-block persists

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THE ACTION OF ADRENALIN IN COMPLETE HEART-BLOCK [1]

By A. RAE GILCHRIST
(From the Clinical Laboratory, Royal Infirmary, Edinburgh)

With Plates 36 to 38

One of the sympathomimetic amines, adrenalin produces striking reactions in the vascular system of the body. Analysis of the response to this drug indicates that its action consists of a highly specific stimulation of the myoneural junctions of the sympathetic system, peripheral vasoconstriction with an associated rise in arterial pressure, and some cardiac acceleration being the predominant features.

Lyon (28) has shown that in man the character of the reaction to adrenalin differs considerably in different subjects. The response, as it affects the cardiovascular system and the metabolism, may be slight, moderate or marked in degree, rapid or slow in its onset, transient, or persistent in its duration. Further, 'the type of reaction depends to a great extent on the rate of absorption of the drug and also on the "sensitiveness" of the patient'. While adrenalin stimulates the accelerator mechanism of the heart, its pronounced pressor effects result in an augmentation of vagal reflexes. Under ordinary conditions an abrupt increase of blood-pressure calls forth reflexes arising in the wall of the first part of the aorta and in the carotid sinus. Reaching the heart by way of the vagus, these reflexes induce some degree of inhibition. After a dose of adrenalin the heart-rate is therefore an expression of at least two interacting forces, direct augmentation of sympathetic origin on the one hand, and reflex vagal inhibition on the other. It is believed that, at least in certain instances, adrenalin also stimulates the vagal centre directly, and if the pre-existing inhibitory tone is high this may result in an actual slowing of the heart (Meek and Eyster (29)). On the other hand, when the vagus tone is low considerable quickening of the heart may result (21).

In this connexion it is of interest to consider the effect of direct sympathetic stimulation in the presence of complete heart-block. The earliest experiments found in the literature are those of Hering (19) who, writing in 1905, reported that while vagus stimulation had little effect on the ventricular rate,

[1] Received June 15, 1933.

sympathetic stimulation was followed almost immediately by definite acceleration of the ventricles. Erlanger (10) obtained similar results. Having produced chronic complete block in dogs, Erlanger and Blackman (11) demonstrated an increase of 22 per cent. in ventricular rate, and 15 per cent. in auricular, on strong sympathetic stimulation in these animals. It is therefore not surprising to find that adrenalin produces an augmentation of the rate and force of the independent ventricular beat at least under experimental conditions. Cullis and Tribe (7), van Egmond (9), Routier (34), Hardy and Houssay (18), and Clerc and Pezzi (5), are all agreed that the administration of adrenalin after the production of complete heart-block in various animals causes an increase in the rate and force of the auricular and ventricular contractions. On the other hand, there is an isolated observation by Kahn (22) who noted the appearance of heart-block in healthy dogs after the intravenous administration of adrenalin.

Three years elapsed before the results obtained in the experimental laboratory were confirmed in cases of heart-block in man. In 1916 Danielopolu and Danulescu (8) reported on the clinical use of adrenalin in complete block. These authors found that after a dose of 1·5 mg. the auricles quickened from 84 to 91 and the ventricles from 30·5 to 40·5. After 2 mg. the respective rates increased from 91 to 120 and from 25·75 to 43·5. In a case of partial block with a two to one frequency full conduction was temporarily restored. Lutembacher (25) administered 0·25 mg. of adrenalin by the intravenous route and noted an immediate acceleration of auricles and ventricles in a patient suffering from complete block. Before the drug was given the rates were 75 and 29. Adrenalin produced a distinct acceleration, the auricular rate reaching 150 and the ventricles rising to 60 per minute. This effect was followed by some irregularity of the ventricular rhythm, with pauses of sufficient duration to account for transient syncopal attacks. For this reason, Lutembacher recommends caution in the use of the drug, and refers to the fact that on several occasions he has observed an extreme slowness of the ventricles on the days following the injection. In the light of modern knowledge it would seem more justifiable to infer that the intravenous route was largely responsible for the dangerous symptoms noted. Subcutaneous dosage is much the safer method of administration. De Graff and Weiss (17) have reported observations on five patients suffering from complete heart-block. Adrenalin was used subcutaneously in doses of 1 to 5 mg., and in each instance an acceleration of the ventricular rate was induced. In one patient no rise occurred in the auricular rate, and on three occasions the acceleration was preceded by a decrease in the rate of the auricles. The fact that the auricles accelerate relatively less than do the ventricles, is attributed by these authors to reflex inhibition acting on the sino-auricular node as a result of an elevation of the arterial blood-pressure. Ventricular extra-systoles were noted to occur frequently after the injection of adrenalin, not only by these authors but also by Lutembacher (25) and Arrillaga (1).

Some conflicting results are found in the literature. For instance,

Strisower (35) has recorded an instance where, after 0·5 mg. of adrenalin, the ventricles not only increased in rate but normal rhythm was temporarily restored. A month later the patient again came under observation and was found to have a partial block with two to one rhythm. A further dose of adrenalin abolished the block for a few seconds. In the case reported by Korns and Christie (23) adrenalin appeared to be the cause of a transition from partial to complete. In association with the increase in the degree of block, the auricular and ventricular rates accelerated, and the rhythm of the auricles became irregular. Parkinson and Bain (32) have described a case in which, when the block was partial, adrenalin facilitated conduction, but when complete, the drug was without effect. Just as the underlying mechanism in the production of partial heart-block varies greatly in the different types of this disorder, so also does the effect of adrenalin on the conducting pathway vary with a number of factors. In partial block, the result of organic disease of the bundle, adrenalin may well produce at least temporary increase of block, either as a result of reflex vagal inhibition, or more probably by the additional burden imposed on the tract in consequence of an increase in the rate of auricular beating. Similarly in partial block of toxic origin, the bundle is often unduly susceptible to vagal influences. Reflex inhibition may then overcome the local tendency of adrenalin to facilitate conduction. On the other hand, in chronic complete block of organic origin it is impossible to believe that adrenalin can restore in the slightest degree the functional link between the auricles and ventricles. The explanation of recovery of conduction after adrenalin may be attributed to the nature of the dissociation. Restoration of conduction may well occur after the use of the drug in intermittent complete block, though not necessarily on account of its use, or in that form of block described by Mobitz (30, 31) as 'dissociation with interference'.

It is only necessary to mention briefly the remarkable effect of adrenalin in the prevention of Stokes-Adams seizures, as this aspect of the use of the drug is not of immediate concern to us. Phear and Parkinson (33) and Feil (13), have reported cases in which repeated seizures were abolished by an increase in the rhythmicity of the ventricular centre so that temporary arrest of the ventricular beat no longer occurred.

The Ventricular Range after Adrenalin

From the preceding review of the literature, it is evident that no systematic study of the effects of adrenalin in complete heart-block in man has been published. De Graff and Weiss (17) in reporting their five cases came to certain conclusions regarding the power of the drug to increase the rate of the human ventricles, but apart from their short review of the subject, and a few case reports, which are often of a meagre nature, little detailed information is available. In the following pages an attempt is made to discover the

nature of the reaction and to determine the factors which govern the response of the heart to this drug.

Twelve cases of complete heart-block have been tested with varying doses of the drug. A technique similar to that employed in the atropine experiments (15) was used, with the exception that the adrenalin was administered subcutaneously, generally on the outer aspect of the left forearm about three inches below the bend of the elbow. Electrocardiograms were recorded at intervals of two minutes for approximately one hour after the injection, and in the majority of the experiments blood-pressure readings were made in the intervals between the exposure of the photographic plates. A period of rest, varying from thirty to sixty minutes, during which the blood-pressure and heart-rates were recorded, served as a control for the adrenalin reaction. Twenty-eight experiments were performed on twelve patients, the dose of adrenalin varying from 0·25 c.c. to 1·0 c.c. of 1/1000 solution (P.D. & Co.). As the drug decomposes rapidly on exposure to light and air, every care was taken to insure the use of a preparation of full potency. The slightest discoloration of the solution is evidence of oxidation, and as the drug deteriorates in keeping, a fresh and reliable supply was used in each test.

In every experiment the rate of the auricles and ventricles was increased by the injection of adrenalin, generally within five minutes of its administration. In spite of the local vasoconstrictor effect at the site of the injection, absorption from the subcutaneous tissue commences immediately, probably by way of the lymphatics (28), and the drug comes into action with surprising rapidity. Lyon (27) found that as a general rule the rise of blood-pressure after a subcutaneous dose of adrenalin commenced within two minutes, and that after nine minutes only about 50 per cent. of the dose remains at the site of injection.

For various reasons the reaction observed to occur after adrenalin is not uniform throughout this series of cases. Atypical results, which demand separate consideration, were obtained in Case 2 (congestive heart failure present), in Case 4 (developed a transient bundle branch-block during the height of the reaction) in Case 7 (one of intermittent complete block) and in Case 12 (transient recovery of conduction under adrenalin). Comparable results were obtained in the remaining eight individuals (Cases 1, 3, 5, 6, 8, 10, 11, and 13), in whom the response to adrenalin was observed under uniform conditions. In the accompanying table, the rates of the auricles and ventricles immediately before the injection of 0·5 c.c. of 1/1000 solution of adrenalin hydrochloride, and the maximum rates attained after the injection are recorded for eight cases of complete heart-block (Table I).

A glance at the table is sufficient to show that the degree of acceleration varies considerably in different cases, and that the magnitude of the reaction as it affects the auricles and ventricles is dissimilar in a given case. With a single exception (Case 1, (*a*)) the ventricular gain in rate expressed as a percentage of the initial rate is greater than the corresponding auricular, thus confirming the observations of De Graff and Weiss (17).

TABLE I

To Show the Maximum Effect of a Subcutaneous Dose of 0·5 c.c. Adrenalin on the Auricular and Ventricular Rates in Eight Cases of Complete Heart-block. Two Cases, Complicated by Auricular Fibrillation are also Included.

Case No. and initials.	Auricular rate.				Ventricular rate.			
	Rate before adrenalin.	Maximum rate after adrenalin.	Gain in auricular rate.	Gain as percentage of initial rate.	Rate before adrenalin.	Maximum rate after adrenalin.	Gain in ventricular rate.	Gain as percentage of initial rates.
1 Mrs. T. (*a*)	70·4	105·0	34·6	49·1	29·2	42·3	13·1	44·9
„ „ (*b*)	75·3	92·6	17·3	23·0	25·0	39·1	14·1	56·4
3 D. C.	72·8	77·6	4·8	6·7	38·5	43·2	4·7	12·3
5 A. H.	58·0	69·8	11·8	20·3	30·6	41·6	11·0	35·9
6 J. W.	51·5	66·8	15·3	29·7	27·4	37·2	9·8	35·8
8 J. B.	Auricular fibrillation			—	32·9	39·7	6·8	20·7
10 Mrs. C.	„	„		—	26·6	42·9	16·3	61·3
11 Mrs. D. (*a*)	90·0	96·8	6·8	7·6	45·2	50·5	5·3	11·7
„ „ (*b*)	98·6	99·3	0·7	0·8	51·0	52·4	1·4	2·7
13 Mrs. H.	76·1	82·9	6·8	8·9	41·7	45·6	3·9	9·4

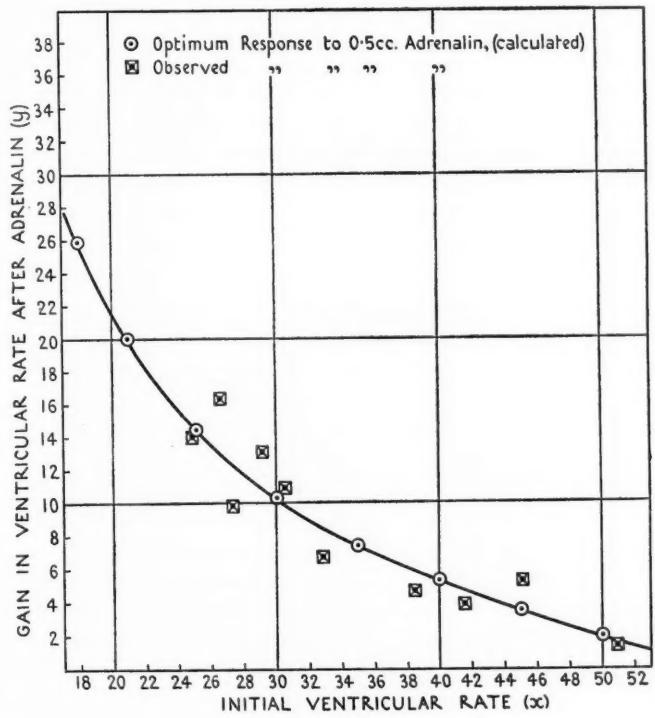
⊙ Optimum Response to 0·5cc. Adrenalin, (calculated)
⊠ Observed „ „ „ „
GAIN IN VENTRICULAR RATE AFTER ADRENALIN (y)
INITIAL VENTRICULAR RATE (x)
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38
18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52

CHART 1.

Closer study of the results obtained for the ventricles reveals that in general less acceleration occurs in those instances in which the resting ventricular rate is high, than in those in which the rate is low before the injection is given. For instance, in Case I (*b*) the initial ventricular rate was 25·0 per minute and the maximum recorded was 39·1 representing a gain of 14·1 beats per minute or an increase of 56·4 per cent. On the other hand, in Case 11 (*b*) the respective rates before and after the injection were 51·0 and 52·4 respectively, an increment of 1·4 beats per minute or only 2·7 per cent. By plotting initial rate against the corresponding gain, a remarkable relationship becomes at once evident. This is shown in Chart 1, in which the results obtained in ten experiments are inserted.

It is obvious that the rate of the ventricles at the time the drug is administered is an important factor in determining the response to a given dose. The plottings lie along a curve which gradually approximates to the base line as the rate 50 is approached, and moves away from the base line with increasing rapidity as lower initial rates are encountered. In other words, the slower the ventricles the greater is their response to a dose of adrenalin and vice versa. This peculiar feature of the adrenalin reaction has not been previously described, and is in sharp contrast to that noted under the influence of atropine (15).

The lie of the plottings suggests that the effect may be represented by a descending exponential curve. This has been tested by plotting the exponential values for the observed increment against the corresponding initial rate. If the observed increments be of the order of a falling exponential curve, then on plotting their corresponding exponential values against the initial rate, the points will fall along a straight line. The data are presented in Table II, and are plotted in the accompanying Chart (2). Let $x =$ the initial rate and $y =$ the observed increment at that rate. The value e^{-y} is taken from exponential Tables.

TABLE II

x	y	e^{-y}
29·2	13·1	2698
25·0	14·1	2441
38·5	4·7	6250
30·6	11·0	3329
27·4	9·8	3753
32·9	6·8	5066
26·6	16·3	1959
45·2	5·3	5886
51·0	1·4	8693
41·7	3·9	6770

The value e^{-y} plotted against x yields a series of points which approximate to a straight line. The fit is not perfect, but is sufficiently good to indicate that the response to adrenalin for varying initial rates closely resembles a decreasing exponential curve. In other words, the reaction approximates to a series of decreasing exponentials for increasing initial rates. The regression line, drawn to the formula $e^{-y} = 2{\cdot}35\,x - 4{\cdot}51$, yields optimum values for e^{-y}

at a given initial ventricular rate (x). Values for y, obtained from exponential tables, have been plotted in Chart 1 where they form a curve, which expresses the theoretical increment for a given initial rate.

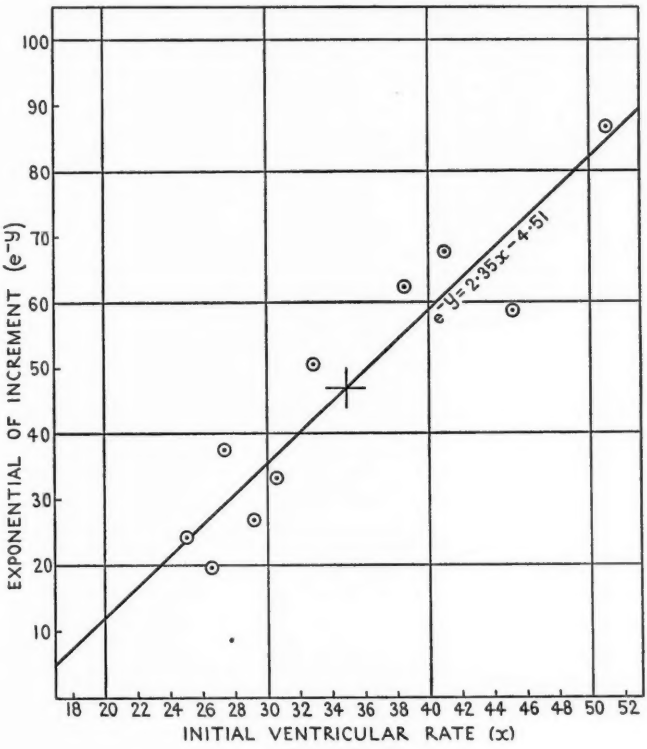

CHART 2.

The Influence of the Size of the Dose on the Ventricular Response.

The results so far examined were obtained with a uniform dose of 0·5 c.c. of adrenalin administered subcutaneously. It is of interest to discover the effect of smaller and larger doses on the response of the ventricles. Doses of 0·25, 0·75, and 1·0 c.c. were tested in those subjects who had on other occasions received 0·5 c.c., and the results are arranged in Table III.

By again plotting the initial rate against the observed gain for each dose, a remarkable result becomes at once evident. This is shown in Chart 3, in which, by way of contrast, the reactions to 0·5 c.c. adrenalin are also included. The continuous curve indicates the optimum response to 0·5 c.c., and it is at once evident that in spite of varying the dose the effect remains remarkably constant. The points representing doses other than 0·5 c.c. fall sufficiently close to the curve to indicate that the exponential expression, representing the effect of 0·5 c.c. also records the effect of 0·25 c.c., 0·75 c.c., and 1·0 c.c.

TABLE III

To Show the Effect of Various Doses of Adrenalin at Different Ventricular Rates.

Adrenalin dosage.		0·25 c.c.			0·75 c.c.			1·0 c.c.		
Case No. and initials.		Initial ventricular rate.	Gain in rate.	Gain as percentage of initial rate.	Initial ventricular rate.	Gain in rate.	Gain as percentage of initial rate.	Initial ventricular rate.	Gain in rate.	Gain as percentage of initial rate.
1	Mrs. T.	26·6	14·9	56·0	23·8	20·2	86·7	21·0	19·4	92·4
3	D. C.	40·4	4·1	10·2	—	—	—	—	—	—
5	A. H.	—	—	—	36·0	7·4	20·6	—	—	—
6	J. W.	—	—	—	—	—	—	25·0	16·9	67·6
11	Mrs. D.	43·0	2·1	4·9	—	—	—	—	—	—
13	Mrs. H.	—	—	—	44·6	2·0	3·8	—	—	—

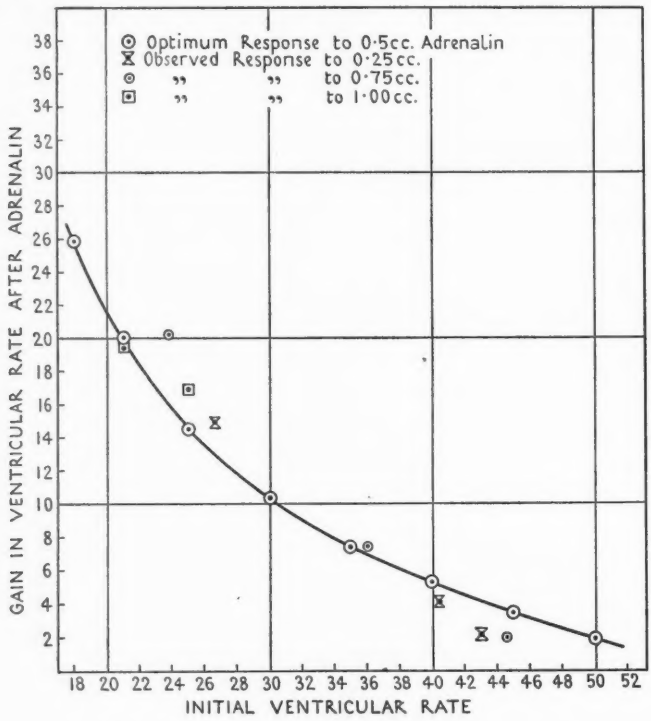
Optimum Response to 0·5cc. Adrenalin
Observed Response to 0·25cc.
" " to 0·75cc.
" " to 1·00cc.
GAIN IN VENTRICULAR RATE AFTER ADRENALIN
INITIAL VENTRICULAR RATE
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38
18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52

CHART 3.

The data, just presented may be interpreted in a number of ways. It seems clear that within a range extending at least from 0·25 to 1·00 c.c. the degree of the reaction depends, not on the size of the dose, but on the initial rate. In other words, the state of the heart at the moment determines its response, and within the usual therapeutic range, the size of the dose is virtually immaterial. It therefore appears that 0·25 c.c. (or perhaps less) will produce as much ventricular acceleration as 1·00 c.c. at a given rate.

The Nature of the Action of Adrenalin on the Ventricular Pacemaker.

In certain respects the observations just described are in accord with the laws governing the activity of enzymes. It is well known that the action of enzymes depends upon their rate of diffusion, and adsorption of substrate on their surfaces. This is followed by the chemical reaction. Bayliss (2) has aptly employed the following illustration.

'Imagine a number of snails in the neighbourhood of a strawberry. As soon as a snail, in the course of its wanderings, becomes sensible of the presence of the food it proceeds towards it. This is the preliminary diffusion. . . . The next stage, that of adsorption, follows rapidly as the animal attaches itself to the fruit. If nothing more happens, there is no chemical reaction. The final, chemical stage is the devouring of the food and its subsequent hydrolysis. It is obvious that the rate of this final stage is proportional to the number of snails "adsorbed". It will also be noted that it is not in linear ratio to the number at work. The more there are, the more they interfere with one another, and when the strawberry is completely covered, the advent of more snails will not further increase the rate of disappearance, since the newcomers cannot get at the fruit. The strawberry here corresponds to the enzyme; we may imagine that, instead of the fruit, we have a powerful chemical substance which induces the disintegration of the snails, representing the substrate, which are adsorbed on its surface.

'The exponential ratio of the concentration of the enzyme to its activity receives a satisfactory explanation on its adsorption theory as will be plain from the above illustration.'

What is true of enzyme action also applies in some measure to the response of the idio-ventricular rhythm to a dose of adrenalin. To draw a comparison it is only necessary to regard the snail, of Bayliss' illustration, as a minimal dose of adrenalin. Up to a point the reaction will be intensified as the dose is increased, but the relationship between the two is not a simple linear expression, and a stage is ultimately reached when a further increase of dose produces no appreciable effect in the degree of reaction. The independence of the response to the size of the dose (within a certain range) suggests that a surface action is involved, and that adrenalin (like the snails of Bayliss' illustration) is being absorbed on some (? enzyme) surface, as an essential condition of its action. Such a surface could adsorb only up to a certain amount of adrenalin, and any excess of the drug would be without further action on that surface. As a similar state of affairs, the action of the enzyme invertase on cane sugar may be instanced (Bayliss (3)). With very low concentration of sugar, the rate of the hydrolysis in the presence of the enzyme varies in a logarithmic way with the concentration of sugar. The sugar is adsorbed on the enzyme surface, but there is not enough to cover it completely, and the reaction

$$E + S \rightarrow ES$$

is governed by the law of mass action. When, however, the sugar concentration

is increased beyond a certain limiting value, the surface is completely covered, and the rate of hydrolysis becomes independent of the sugar concentration, so that addition of still more sugar has no effect on the reaction.

That this peculiar effect of adrenalin is not limited to the ventricles is borne out by the observations of Lyon (26) on its action on the blood-pressure. It was found that the amount of the rise of blood-pressure after uniform doses of adrenalin, depended upon the level of the blood-pressure at the moment of injection, a small rise occurring if the initial pressure were high and vice versa. A study of the response of the ventricles in complete heart-block reveals that the reaction to adrenalin is similar in nature to that observed by Lyon under experimental conditions (see Clark (4)).

The Response of the Auricles.

It has been shown above that the ventricles increase in rate after an injection of adrenalin, and that the amount of acceleration induced depends upon the pre-existing rate. Further, for doses ranging in size from 0·25 to 1·0 c.c. the gain in rate is uniform, provided the initial rate is constant. The peculiar character of the ventricular response to adrenalin makes it desirable to inquire into the behaviour of the auricles under similar conditions. In complete heart-block the ventricles are functionally isolated from the auricles, and are therefore no longer under the dominating influence of the normal pacemaker—the sino-auricular node.

In each of the individuals studied, adrenalin produced some auricular acceleration. The amount varied considerably in different cases. The responses of the auricles to 0·5 c.c. in eight instances are shown in Table I, and to 0·25, 0·75, and 1·0 c.c. in Table IV.

TABLE IV

To Show the Effect of Various Doses of Adrenalin at Different Auricular Rates.

Adrenalin dosage.		0·25 c.c.			0·75 c.c.			1·0 c.c.		
Case No. and initials.		Initial auricular rate.	Gain in rate.	Gain as percentage of initial rate.	Initial auricular rate.	Gain in rate.	Gain as percentage of initial rate.	Initial auricular rate.	Gain in rate.	Gain as percentage of initial rate.
1	Mrs. T.	80·8	22·0	27·2	81·8	41·2	58·5	69·0	45·0	65·2
3	D. C.	78·1	9·7	12·4	—	—	—	—	—	—
5	A. H.	—	—	—	59·0	? 41·0	? 69·5	—	—	—
6	J. W.	—	—	—	—	—	—	54·7	19·4	36·0
11	Mrs. D.	89·8	3·7	4·1	—	—	—	—	—	—
13	Mrs. H.	—	—	—	74·5	6·4	8·6	—	—	—

By employing similar methods of analysis it is found that there is not such a close relation between the amount of auricular acceleration and the initial auricular rate. The response appears to vary considerably, not merely from a given resting auricular rate, but also to some extent for the amount of the

drug employed. The points when plotted show a somewhat wider 'scatter' than those expressing the ventricular ratio. It would therefore appear that the reaction of the auricular tissue differs to some extent from that displayed by the ventricular. Actually, this disparity is perhaps more fictitious than real.

It may very well be that the auricular response to adrenalin is not inherently different from that of the ventricles, but that the reaction in the former is modified or distorted by certain extraneous influences playing upon the sino-auricular node. It has already been pointed out that in normally beating hearts the reaction to this drug is profoundly influenced by inhibitory vagal reflexes. There is no reason to believe that the normal reflexes arising in the carotid sinus or arch of the aorta are appreciably disorganized in the presence of complete heart-block, and it may therefore be assumed that the rise of pressure, consequent upon the injection of adrenalin, will call forth inhibitory reflexes acting on the sino-auricular node. The rhythmicity of the pacemaker and the degree of vagal tone must be important factors in modifying the natural tendency of the auricles to accelerate in response to adrenalin.

The Relation of the Auricular to the Ventricular Response.

Though it has not been possible to demonstrate a high degree of correlation between the gain in rate of the auricles and their initial level, yet nevertheless there is a distinct relation between the auricular gain in rate and the associated ventricular acceleration. The fact can be demonstrated in a number of ways.

Perhaps the simplest method is to plot the respective increments, each as a percentage of the pre-existing rate, one against the other. This has been done in Chart 4. Study of this diagram reveals that the percentage increments for auricles and ventricles after adrenalin are not proportionate. For instance, when the ventricles accelerate by, say 50 per cent., the auricles do not quicken by the same amount, but rather less. If the magnitude of the reaction was similar in auricles and ventricles then the points would fall along the line A. Actually, they appear to fall along the line B. This implies that as the percentage ventricular acceleration increases, the corresponding auricular gain lags more and more behind. It has already been shown that the greatest gain in ventricular rate occurs from the lowest initial levels. This must mean that under such conditions, when the rate and force of ventricular systole are greatly increased, a mechanism comes into play which has the effect of limiting the auricular response. In other words, it would appear probable that the widening interval separating the lines *A* and *B* represents the effect of increasing reflex vagal tone. As the magnitude of the ventricular reaction increases so also does reflex vagal tone. The probable mechanism is, that as the ventricular rate and the blood-

pressure rise, inhibitory vagal reflexes limit the auricular response. The more the ventricles gain in rate, the greater is the lag in the auricular response.

The same phenomenon may also be demonstrated by contrasting the percentage gain in rate of auricles with that of the ventricles when each is plotted against the initial *ventricular* rate as shown in Chart 5. The respective plottings lie along two distinct curves, that for the ventricles being

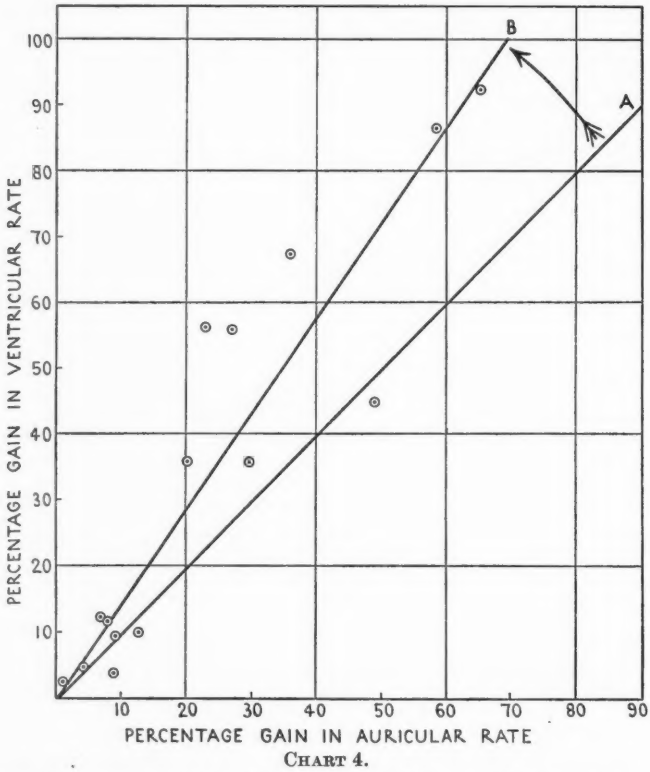

CHART 4.

almost a perfect exponential relationship to the pre-existing rate. At high initial rates the curve for the auricular acceleration lies nearer the base line than the ventricular. As low initial rates are approached the auricular curve displays a slight shift to the left, indicating that the auricular response tends to be restricted. This is confirmed by again plotting the exponentials of the percentage gains in rate for the two chambers of the heart. The ventricular exponentials, as previously shown, are grouped almost in a straight line. The auricular exponentials are less perfect in their arrangement, their line being slightly curved.

It is suggested that the reason for the dissimilarity between the two curves is due to vagal influences. These arise in the carotid sinus and aortic wall as a result of sudden elevation of the arterial pressure, and have the effect of retarding the auricular rate. The degree of limitation is apparently

determined largely by the pre-existing ventricular rate, for the greater the degree of ventricular acceleration the more does the gain in auricular rate tend to lag behind the ventricular. It is difficult to suggest an adequate explanation for this observation. The probability is that the limitation of the auricular response is due to vagal influences, and it may be that the auricles beating at a faster rate are relatively more susceptible to inhibition

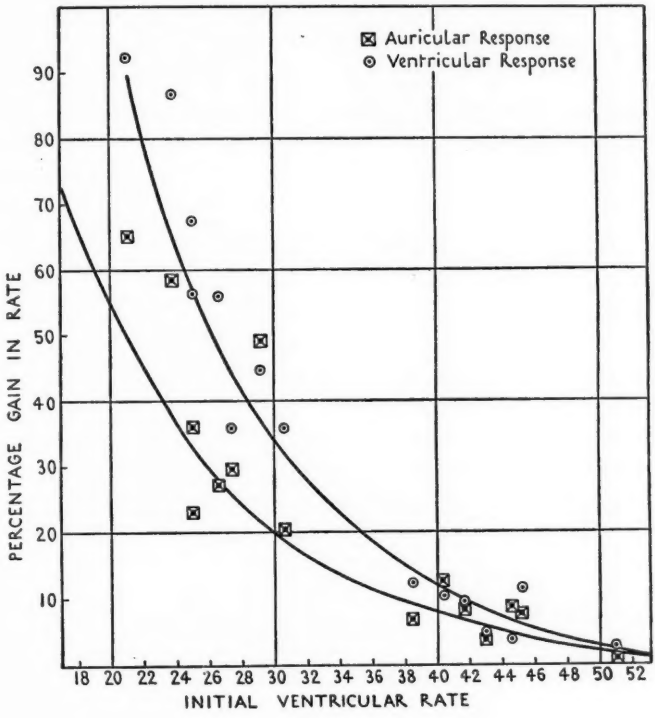

CHART 5.

than the slower ventricular rhythm. It is peculiar that the initial ventricular rate should be a factor in determining a limitation in the corresponding auricular response to adrenalin. The work of Euler and Liljestrand (12) on the circulation rate in man after adrenalin indicates that the drug acts as a whip to the heart, in that the volume flow of blood was increased out of proportion to the oxygen requirements of the tissues. In complete block at the slower ventricular rates the output of blood per beat is probably maximal, and adrenalin, by increasing the rate of the ventricles and maintaining their stroke-volume, may well augment the blood-pressure, even apart from the drug's peripheral vasoconstrictor effects. It may be for this reason that reflex inhibition is induced in greater degree when the initial ventricular rate is low and the increment maximum, than when the initial rate is high and the corresponding gain in rate but slight.

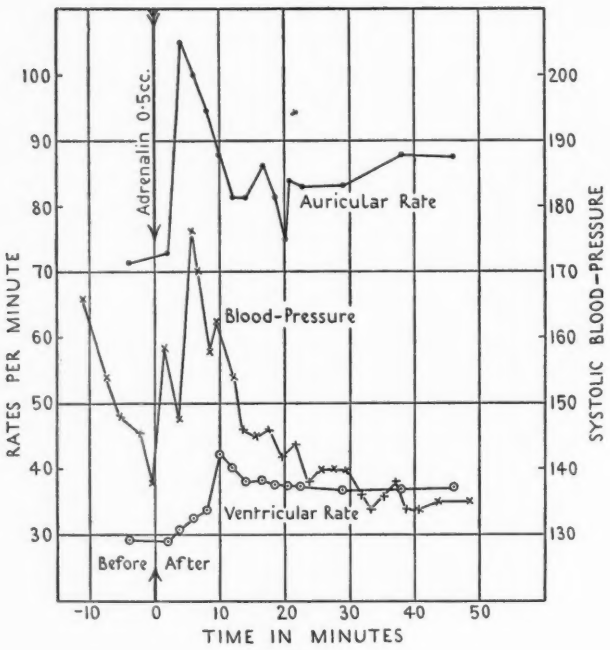

CHART 6.

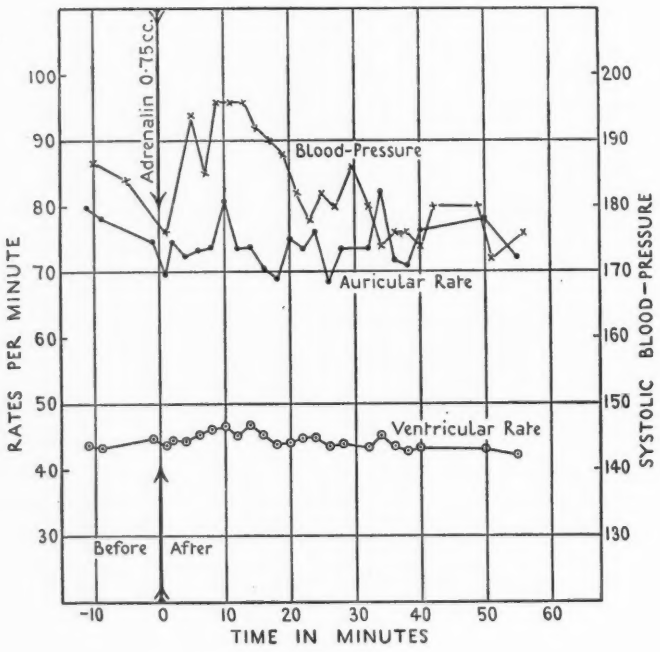

CHART 7.

The Course of the Reaction to Adrenalin.

An examination of the course of the reaction to adrenalin in complete block does not reveal any striking difference from that which has been noted to occur in the normally beating heart. Just as the reaction may be slow or rapid in onset, or transient or persistent in duration, in different healthy individuals, so also in those suffering from complete block, the character of the response varies within wide limits.

It is not necessary to depict in detail the reaction observed in each individual. To demonstrate the extremes observed it is sufficient to select two individuals, one in whom the initial ventricular rate was low, and the other in whom the usual resting rate was high. Cases No. 1 and 13 have been chosen as examples, and the course of the reaction as it affects the systolic blood-pressure, and the auricular and ventricular rates is depicted in the accompanying Charts (No. 6 and 7).

Case 1 (Chart 6) had, after lying at rest for over thirty minutes, a ventricular rate of 29·2, an auricular rate of 70·4, and a systolic pressure of 138 mm. Hg. A very prompt reaction immediately followed the dose of adrenalin. Within four minutes the auricles reached their maximum rate of 105 per minute, from which they gradually declined. It can be seen that three minutes after the auricular rate attains its observed maximum, the blood-pressure reaches its highest point, and three minutes later the ventricular rate, after a more gradual acceleration, touches its greatest level. It is worth noting the different time reactions in auricles and ventricles. The highest peaks in the auricular and ventricular rates do not occur at the same moment. Actually, the auricular rate has attained its greatest value and is declining during the period when the ventricles are gaining most rapidly. From the chart it would appear that the remarkably abrupt acceleration of the auricles between the second and fourth minutes is permitted by a transient fall in blood-pressure. As the systolic pressure increases, the rise in auricular rate is stemmed. The ventricles meantime continue to accelerate. According to Lyon's researches (27) this period corresponds with the time at which the greatest amount of the adrenalin is actually in the blood-stream, and when the amount passing from the blood to the tissues is maximum. Thereafter the blood-pressure declines, reaching its pre-existing level about thirty minutes after the injection. It is noteworthy that the auricular and ventricular accelerations persist for some time after the blood-pressure reaction has passed off.

In Case 13, on the other hand, the initial rates were relatively high, and even after a prolonged rest the systolic pressure was 184 mm. when the adrenalin was administered. Chart 7 demonstrates the course of the reaction in this patient. The response in this woman was of longer duration but of less intensity than that observed in Case 1. The blood-pressure, standing at a higher initial level than in the previous individual, gains less, and the ventricular reaction is also slight. The auricles do not exhibit an early

abrupt acceleration but fluctuate in rate from minute to minute. No untoward symptoms followed the subcutaneous injection of adrenalin, and it produced no distress amongst these patients. In the usual subcutaneous doses the drug may be given in cases of complete block without harm resulting. Levine (24) has employed the drug as a diagnostic test for angina pectoris, on account of the ease with which precordial pain is induced among those who suffer from this cardiac disability. No suspicion of angina occurred in any of these cases of block, although two suffered habitually from precordial pain on exertion. Extra-systoles were occasionally observed. It should be pointed out that they were not included in the estimation of heart-rate. Finally, in not a single instance among these eight patients did adrenalin alter the degree of block.

Atypical Response to Adrenalin

It has been pointed out in previous pages that only eight individuals to whom adrenalin was administered yielded a reaction which was more or less similar throughout the group. A response differing in certain respects from that observed in this group was recorded in four patients (Cases 2, 4, 7, and 12).

In this section it is proposed to examine briefly the reaction in these four individuals. In Case 2, a mild degree of congestive heart failure existed on the two occasions when this man's reaction to adrenalin was tested. He received two doses of respectively 0·25 c.c. and 0·5 c.c. After each the amount of ventricular acceleration exceeded that which would be expected for the corresponding initial heart-rate, and the reaction was a trifle slower in onset, perhaps as a result of the decreased circulation rate and slower absorption of the drug. It is difficult to explain why a heart labouring under the burden of a gross defect in circulation should respond by an excessive acceleration, unless it be that, incapable of increasing its systolic output, an attempt is made to compensate for this by an unusual gain in rate.

In Case 4 the gain in rate was not as high as might be anticipated at the pre-existing rate. Electrocardiograms showed that this man, towards the height of the reaction, developed a bundle branch-block which persisted until after the end of the experimental period. This abnormal rhythm seemed to form a sufficient reason for relegating this patient to the group in whom the response was atypical.

Case 7 is of some little interest in that this man suffered from intermittent complete heart-block. It was possible to test his response to adrenalin on two occasions, on the first of which the block was complete, whereas on the second occasion the block was of the 2 to 1 type with a *P-R* interval of 0·2010 sec. The electrocardiogram (Plate 37, Fig. 1) recorded immediately before the first test shows complete heart-block with a defect in the bundle-branch conduction, with the main deflections downward in Lead 1 and upward

in Lead 3. Until recently this record would be classified as an example of a defect in the left branch of the bundle, but the work of Wilson and his collaborators (36) would suggest that more probably the right branch was the sight of the defect. Records from Lead 3 were made repeatedly during the course of the sixty-four minutes following the injection. Between five and seven minutes after the dose the form of the ventricular complex underwent a complete alteration in form, becoming almost the mirror image of that previously existing. This is shown in Plate 37, Fig. 2. The block of the 'left' branch has been replaced by a block of the 'right' (or vice versa, according to Wilson's theory). This persisted throughout the experiment, and the final records in Leads 1, 2, and 3 are in marked contrast to those existing before the adrenalin was injected. Compare Plate 37, Fig. 1, with Fig. 3.

Alterations in the ventricular complexes in complete heart-block occasionally occur spontaneously, and have been described and analysed in detail by Gilchrist and Cohn (16). We observed gradual transition in the form of the Q.R.S. waves in cases of complete heart-block, so that while left ventricular effects might predominate at one time, in a few seconds right-sided influences took their place. An example of a spontaneous and temporary change in the form of the ventricular complex is shown in Plate 36 (Case 8 of the present series). We came to the conclusion that the phenomenon was due to two interacting centres of impulse production, one on either side of the heart. This theory assumes the presence of a bilateral bundle lesion, not necessarily of an organic nature, with rhythmic centres below the defect. 'In this case, the simultaneous discharge of impulses from each centre will result in a composite complex of normal outline. By a disturbance of this time relationship the centre of impulse production in advance of the other assumes control and the resulting complexes are of the form associated with a preponderance of right or left-sided effects as the case may be.' The other possibility, originally proposed by Cohn, is that abrupt transitions in the form of the ventricular complexes might be interpreted as the onset of partial bundle branch-block in one branch with simultaneous recovery of conduction in the other branch. A change in the form of complexes after adrenalin was noted on two occasions in one heart-block patient by de Graff and Weiss (17). In health, according to Clough (6), epinephrine does not alter the *P-R* conduction time in man, probably for the reason that, though an increase in accelerator tone facilitates conduction, the reflex vagal stimulation induced by adrenalin, will tend to counterbalance the pure sympathetic effect. In the case under consideration, it is unlikely that vagal tone induced the change in the form of the ventricular complexes, for it persisted long after the blood-pressure had returned to its pre-existing level. It would therefore seem more probable that the change in the conduction defect from one side of the heart to the other resulted from a change in the time relationship between two pacemakers. This might result from exhaustion of one branch or centre as a consequence of an increased rate of stimulus production. An increase in the refractory period of the associated

bundle-branch may ultimately be dependent on a blood-supply inadequate for the immediate needs of the over-stimulated tissues.

By the following day the rhythm of the heart in this patient (Case 7) had changed spontaneously, 2 to 1 block now replacing the complete, which had previously been present. It is of interest to note that the partial recovery of conduction was accompanied by not only a further change in the form of the ventricular complexes but also by a peculiar inversion of the *P* waves in all leads. This is shown in the electrocardiogram (Plate 38, Fig. 4) taken immediately before the injection of 1·0 c.c. adrenalin. Two minutes later conduction was abolished, the block became complete, the ventricular complexes changed in form, and the *P* waves became upright (Plate 38, Fig. 5). The block remained complete for eighteen minutes, the main ventricular deflection being upright. Twenty minutes after the injection conduction was restored, the ventricular complex changing its shape in association with the alteration in rhythm. In Lead 3 the main deflection was upright during complete block, and downward throughout the period of 2 to 1 block. Nevertheless, Leads 1, 2, 3 (Plate 38, Fig. 6), taken an hour after injection, show that though 2 to 1 block persists, yet the form of the complexes is different from that observed during the 2 to 1 block, which was present before the injection was given.

Several other individuals showed transient and often abrupt changes in the form of the ventricular complexes a few successive cycles after adrenalin administration, and not at other times, though several hundred electrocardiograms were recorded. Atropine, for instance, did not affect the form of the ventricular waves in a single instance. It therefore seems reasonable to suppose (in spite of the fact that Case 7 suffered from spontaneous changes in conduction) that the alterations observed to occur after adrenalin were in all probability due to adrenalin. To carry this argument a stage further, it may be tentatively suggested that the spontaneous alterations in conduction, which occurred on more than one occasion, might well be determined by some subtle alteration in accelerator tone and in the local blood-supply. This man's heart seemed unduly susceptible to adrenalin, but whether this or some other closely-related substance of bodily origin determined the apparently spontaneous onset of complete block must remain a mystery. It is known that adenosine may produce a transient block in man (20), and perhaps one explanation of intermittent complete heart-block is ultimately to be found in the addition to the blood-stream of a subtle chemical substance of bodily origin.

The response of Case 12 to adrenalin is briefly discussed under functional *a-v* dissociation (14).

Summary and Conclusions

Twelve cases of complete heart-block have been tested with repeated subcutaneous doses of adrenalin in an attempt to discover the factors which govern the response of the heart to this drug.

After a subcutaneous dose the drug comes into action with surprising rapidity. Acceleration of auricles and ventricles may occur within two to four minutes of the injection.

The amount of ventricular acceleration induced bears a striking relationship to the rate existing immediately before the injection. High initial rates are followed by little or no gain in rate, slow rates by pronounced acceleration. This means that the state of the heart at the time of the drug's administration determines the heart's response.

By plotting the observed increment against the corresponding initial rate, it is found that for a group of eight cases the reaction approximates to an almost perfect series of decreasing exponentials for increasing ventricular rates.

Within a certain range of dosage, the amount of adrenalin injected makes little or no difference to the ventricular response at a given ventricular rate. The optimum response to 0·5 c.c. adrenalin for various initial rates has been calculated and compared with the reaction observed after doses of 0·25, 0·75, and 1·0 c.c. in the same subjects. The gain in rate after these doses is to all intents similar to that recorded after 0·5 c.c. This implies that the response of the heart is determined, not by the size of a dose in the usual therapeutic range, but by the rate of the heart existing at the time of the injection. In other words, for a given initial rate 0·25 c.c. of adrenalin will produce as much acceleration as a dose four times that amount.

This phenomenon is discussed in the light of the known laws which govern enzyme action. The independence of the size of the dose, and the response recorded, suggests that a surface action is involved, and that adrenalin is being adsorbed on some (? enzyme) surface, as an essential condition of its action.

The observation that the initial rate determines the degree of acceleration finds support in blood-pressure studies. Lyon has suggested that the reaction to adrenalin obeys Weber's law, in that the amount of elevation in the systolic blood-pressure, after uniform doses of adrenalin depended upon its level at the moment of the injection.

It has not been found possible to demonstrate as close a correlation between the initial auricular rate and its increment after adrenalin, as that observed in the case of the ventricles. The auricular response is modified to some extent, particularly in those cases in which the magnitude of the ventricular response is maximum, that is, when the initial ventricular rate is relatively low.

It would appear probable that reflex vagal influences, induced by a marked ventricular reaction, limit the auricular response. The amount of limitation is apparently determined largely by the initial ventricular rate.

The course of the reaction to a subcutaneous dose of adrenalin varies as much in complete block as it does in the normal beating heart. The maximum auricular and ventricular reactions are not necessarily synchronous. As a general rule the auricles attain to the height of their

reaction before the ventricles have completed their acceleration. An increased frequency of both chambers of the heart persists after the blood-pressure rise has returned to its pre-existing level. No untoward symptoms resulted from the use of the drug. Release from the block was not observed in any of the experiments performed upon these eight patients.

Reactions differing from those just described were encountered in four patients. One of these cases was a man who suffered from intermittent complete block. Tested with adrenalin during complete block no change in the rhythm occurred, but a branch defect changed from one side of the heart to the other. Tested during 2 to 1 rhythm, complete block was induced. The direction of the main ventricular deflection varied according to the presence or absence of conduction through the main stem of the bundle. During half-rhythm the ventricular complex in Lead 3 was directed downwards, whereas during complete dissociation its direction was upwards. The fact that this man's heart was unduly susceptible to adrenalin suggests that in cases of intermittent complete heart-block, the temporary failure of conduction, leading to transient complete dissociation, may perhaps be associated with the formation within the body of some subtle and complex chemical substance analogous to adrenalin or adenosine.

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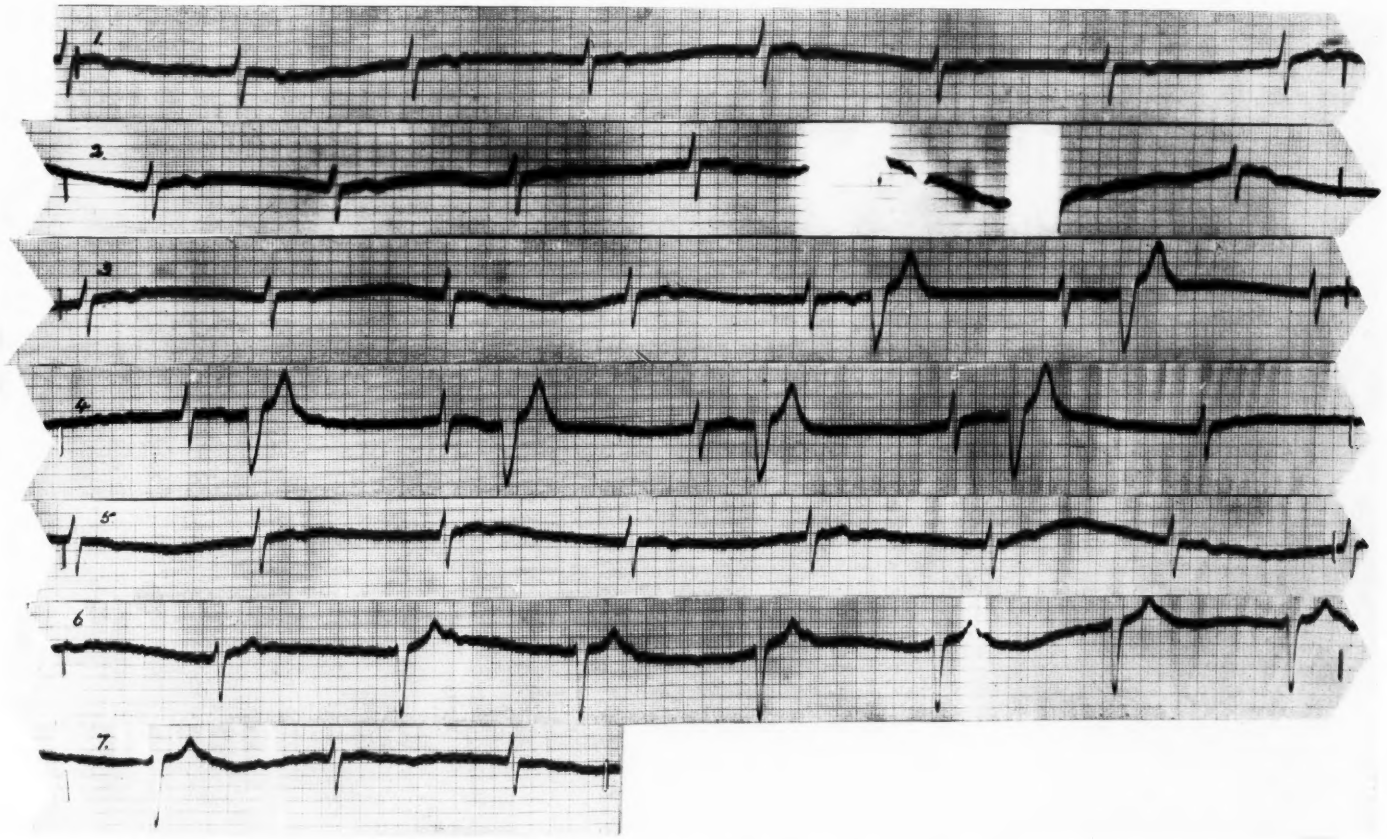

Plate 36 shows a continuous film record taken from Case 8 after a prolonged rest on a couch. It illustrates the spontaneous occurrence of a change in the form of the ventricular complexes. After a short run of coupled rhythm, as shown in strips 3 and 4, a gradual change takes place in the size and shape of the ventricular complex. In strip 6 there are seven complexes which differ from those in strip 5. The usual form of the Q.R.S. group reappears in strip 7

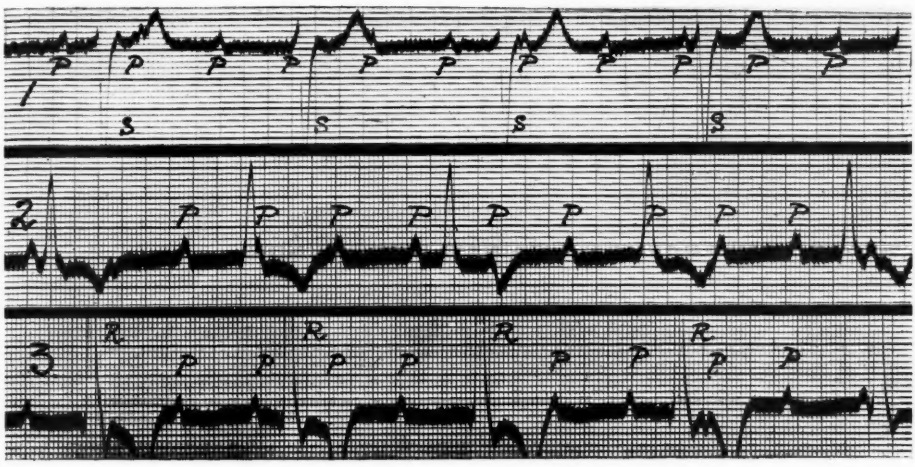

FIG. 1

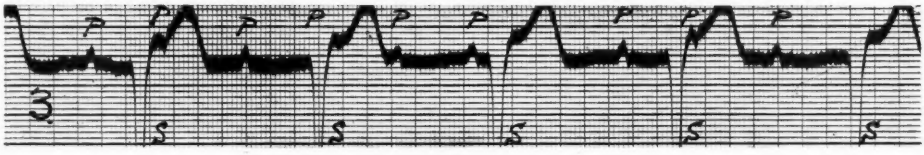

FIG. 2

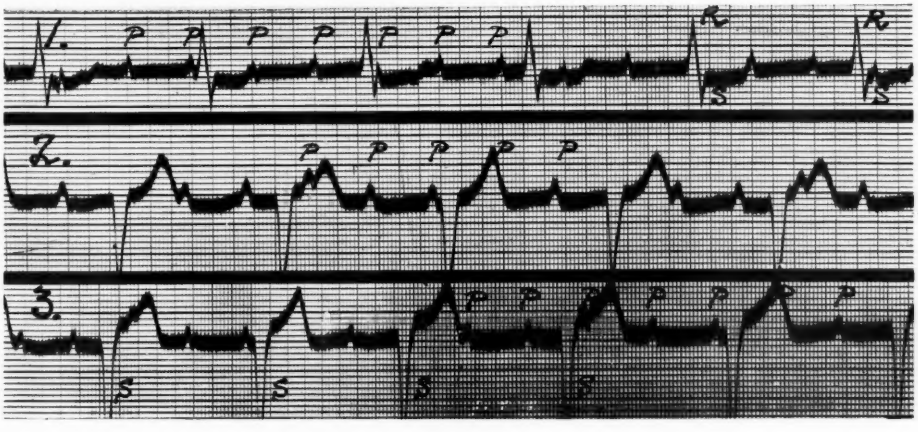

FIG. 3

Figs. 1, 2, and 3 are electrocardiograms taken from Case 7 during the course of an adrenalin test. Fig. 1, taken before the injection, shows complete heart-block. Between five and seven minutes after the dose the form of the ventricular complex changed as shown in Fig. 2. One hour after the injection Leads 1, 2, and 3 (Fig. 3) are in marked contrast to those existing immediately before the drug was administered (Fig. 1)

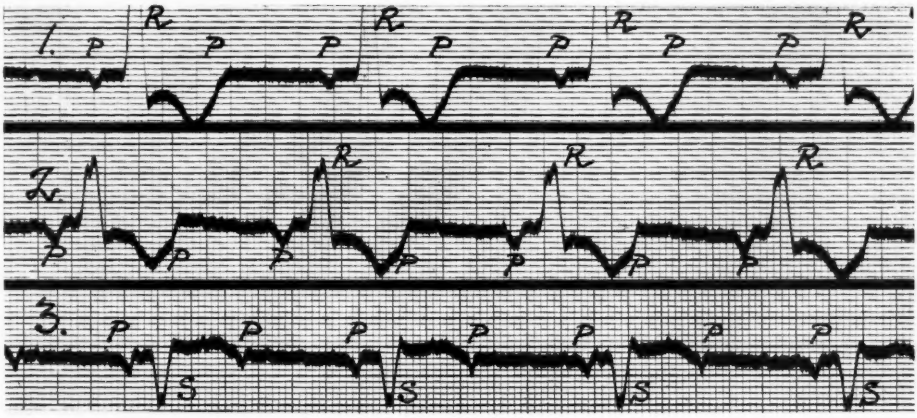

FIG. 4

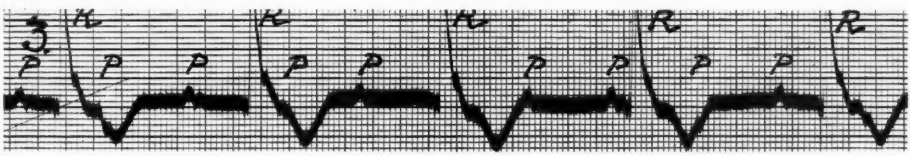

FIG. 5

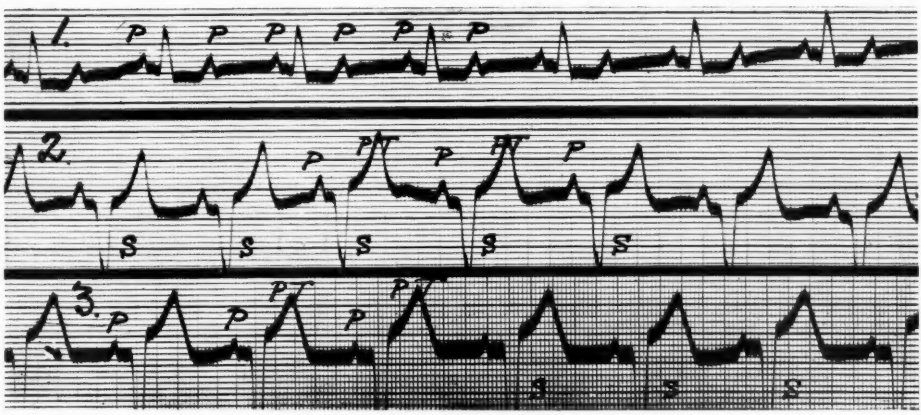

FIG. 6

Figs. 4, 5, and 6 are electrocardiograms recorded on the following day from the same patient, Case 7. Fig. 4, photographed before the administration of 1·0 cc. of adrenalin, shows the presence of 2 to 1 block with a further change in the form of the Q.R.S. group. Two minutes after the injection the block became complete (Fig. 5) and the complexes in Lead 3 reverted to the form depicted in Fig. 1. For eighteen minutes the block remained complete. Twenty minutes after the injection, 2 to 1 conduction was restored, the ventricular complex changing its shape in association with the alteration in rhythm (Fig. 6)

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DESCRIPTION OF CHARTS

CHART 1. To show the maximum gain in rate induced by 0·5 c.c. of adrenalin at various initial rates. The slower the ventricular rate the greater is the response to adrenalin, and vice versa.

CHART 2. To show that by plotting the exponential value of the observed increment against the initial ventricular rate, the points thus obtained approximate to a straight line. This indicates that the response to adrenalin closely resembles a series of decreasing exponentials for increasing initial power rates.

CHART 3. To show that the response observed after doses of 0·25, 0·75, and 1·00 c.c. adrenalin lies sufficiently close to the optimum response to 0·5 c.c. to indicate that, in spite of variations in the dose, the observed effect remains remarkably constant for a given initial ventricular rate.

CHART 4. To show that in a given individual auricular and ventricular accelerations are not of equal magnitude. If the percentage increments were similar then the points would fall along the line *A*. The line *B* approximates to the observed response indicating that the percentage gain in ventricular rate exceeds the corresponding auricular increment.

CHART 5. To show that, when the response of auricles and ventricles are plotted against the initial *ventricular* rate, the auricular increment displays a slight shift to the left, indicating that the auricular response tends to be more and more restricted the lower the initial ventricular rate.

CHART 6. To show the course of the response, as it affects the auricular and ventricular rates and the systolic blood-pressure in Case 1.

CHART 7. To show the reaction observed in Case 13.

616.61–002
616–005.98

OEDEMA IN NEPHRITIS[1]

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Ever since the days of Bright (2) the pathogenesis of oedema in nephritis has given rise to much discussion. Bright, himself, associated the oedema with a reduction in the protein of the blood-serum, thus approximating, in a general way, to the view which is gaining ground to-day. In 1838 Solon (26) suggested that hydraemic plethora was an important factor in the causation of nephritic oedema. Since then this hypothesis has been elaborated; many investigators held the belief that this increase in water content of the blood was due to inability of the kidney to excrete water, and resulted in elimination of water from the blood-stream to the tissues in an effort to preserve the blood volume within normal limits. This conception, however, must be abandoned in view of the fact that modern methods have demonstrated that there is no increase of blood volume associated with oedema either in acute or chronic nephritis.

In 1909 Strauss (28) and Widal (31) pointed out that oedema increased after administration of sodium chloride to a patient with renal oedema, whereas withdrawal of salt from the diet led to diuresis and disappearance of the oedema. The conclusion was drawn that the prime factor in oedematous conditions associated with nephritis was an inability of the kidney to excrete salt, which resulted in retention of water to keep the salt concentration of the tissue fluids within normal limits. It must be remembered, however, that none of the numerous investigators of this problem has detected any relationship between degree or incidence of oedema and the level of the blood or plasma chloride, as one would have expected if renal inefficiency in the excretion of chloride was an important factor. Indeed, blood chloride rarely shows significant variations in nephritic patients with oedema. An even more convincing argument against this hypothesis is the fact that anuric conditions, arising from urinary obstruction, are associated with a high blood chloride but not with oedema.

Fischer's (8) conception of oedema is that of intracellular imbibition of fluid by the tissue colloids under the influence of acid production in the tissues. No apparent relationship, however, has been shown between oedema and acidosis. Furthermore, since fluid occurs free in the serous cavities,

[1] Received July 17, 1933.

and oedema shifts under the influence of gravity, and can be drained by acupuncture, this supposition is hardly tenable.

A still later view is that of Volhard and Fahr (30), who believe that the oedema of nephrosis is due to increased permeability of the capillaries caused by a toxic substance elaborated by the degenerating epithelium of the kidney tubules. Oedema in glomerulo-nephritis they attribute to the same factor arising from secondary tubular degeneration. Since the capillaries are normally permeable to water and electrolytes, increased capillary permeability must mean that the wall of the capillary is damaged. As Peters (20) says, good evidence of the intact state of the capillary wall is given by the fact that oedema fluid in these conditions contains 0·5 gm. per cent. or less of protein, while if the capillary wall were abnormally permeable, protein would almost certainly be in greater concentration in the effused fluid.

In 1895 Starling (27) pointed out the cardinal importance of the serum proteins in the maintenance of fluid balance between the blood and the tissues, and the fact that the inorganic constituents of the serum could not exert any osmotic pressure on account of their ability to pass through the normal capillary wall into the tissues. Epstein (7) applied these views to explain the production of oedema in chronic parenchymatous nephritis and in the syndrome termed nephrosis, and stated that oedema resulted from a fall in serum proteins, which was due to long-continued proteinuria. Govaerts (10), and Schade and Claussen (25) estimated the osmotic pressure exerted by serum proteins in the normal subject to be about 29 mm. Hg., a pressure which lies between arterial and venous blood-pressure. This pressure, as Govaerts showed, is not exerted equally by the components of the serum protein, albumin and globulin, the former having a smaller molecule, and therefore exerting greater osmotic pressure, than the latter. Therefore the estimation of total serum protein does not give an indication of the osmotic pressure. Govaerts found the respective pressures to be (*a*) albumin 5·5 mg. Hg. per grm. per 100 c.c., and (*b*) globulin 1·4 mg. Hg. per grm. per 100 c.c.

According to Starling's view, protein osmotic pressure is antithetic to hydrostatic pressure in the capillaries, so that decrease in serum protein or increase in hydrostatic pressure both conduce to oedema formation. The level of serum total protein at which oedema becomes manifest is not constant, chiefly because of differences in the proportions of albumin and globulin present, but also because of varying hydrostatic pressure in blood-vessels and of tissue elasticity, which two factors act in opposite directions.

Lending support to this theory of the pathogenesis of oedema is experimental evidence obtained by plasmapheresis, first performed by Leiter (14), Barker and Kirk (1), and Darrow and co-workers (6). In these experiments dogs were bled and the corpuscles replaced suspended in saline instead of plasma. After a certain number of tranfusions of this nature oedema becomes obvious. It occurred with regularity when serum proteins had fallen to a level somewhat lower than that associated with nephrotic oedema in

man, the critical level of osmotic pressure being about 12 mm. Hg. (Darrow).

Nutritional oedema, of which mention will be made subsequently, is also associated with a low level of serum proteins. Rise in serum proteins and disappearance of oedema occur coincidentally on recovery.

Although the importance of salt in the production of oedema has been amply confirmed, salt occupies but a secondary position in regard to aetiology. The problem seems to be rendered more easily understood if the reaction of a normal subject to administration of sodium chloride and water is considered. If either salt or water is given alone, rapid excretion occurs without retention of water and rise in weight. If, however, salt and water are given together, some retention occurs with rise in body weight (Cohnheim et alii (5)). In chronic renal oedema the same phenomena occur, but the retention following administration of salt and water together is much greater. This is due to the fact that in this condition the serum osmotic pressure of the blood is reduced, and consequently water cannot be retained in it as well as in health. For the formation of oedema a quota of salt is required, but the tendency for oedema formation must be present in the shape of lowering of osmotic pressure due to reduction of serum proteins. It seems an indisputable fact that if oedema is present in nephritis, excluding acute nephritis and the cases where oedema is due to cardiac failure, serum proteins are invariably reduced. Moreover, the presence of oedema is usually associated with a certain low level of these proteins (Moore and Van Slyke (17), Van Slyke and co-workers (29), Peters and co-workers (22), and others). In nutritional oedema no kidney lesion is present, but the serum proteins are likewise consistently below normal. In dogs subjected to plasmapheresis no definite kidney lesion is found at autopsy by a large majority of investigators. It would, therefore, appear probable that the kidney *per se* has no direct responsibility in the formation of oedema in chronic Bright's disease, since it is possible for oedema, due to reduction in serum protein, to occur without a demonstrable kidney lesion in nutritional oedema and in dogs subjected to plasmapheresis.

Writers on the subject seem unanimous that it is impossible to include the oedema of acute nephritis within Starling's theory of pathogenesis, since it may occur with serum proteins, which are little, if at all, below normal level. The possibility of the application of Starling's theory to explain the causation of dropsy in acute nephritis is considered at a later stage in this communication.

In this paper the problem of the pathogenesis of oedema in nephritis is approached from the standpoint afforded by Starling's conception of oedema formation, which has been briefly discussed in the foregoing pages. For purposes of analogy and comparison, I have included a number of cases of cardiac and nutritional oedema. All the cases were children between two and thirteen years of age, a circumstance of advantage in so far as the clinical picture of nephritis was unclouded by cardiac or arterial disease.

After a fast of at least four hours, blood was withdrawn with minimal stasis. Serum proteins were determined by Howe's (11) micro-Kjeldhal method, and albumin and globulin separated by Howe's technique. Non-protein nitrogen was estimated by the method of Folin and Wu (9). Serum osmotic pressure was calculated from Govaert's formula

$$(5{\cdot}5 \times \text{albumin in grm. per cent.}) + (1{\cdot}4 \times \text{globulin in grm. per cent.}) = \text{serum osmotic pressure in mg. Hg.}$$

To indicate the degree of oedema by clinical estimation, the following symbols are used:

0 = None.
∓ = Puffiness of face. No pitting.
+ = Subcutaneous oedema. Pitting.
+ + = Marked pitting. Effusions.

Normal Controls

Serum proteins were estimated in twenty apparently normal children, aged between 2 and 13 years. The series included patients convalescent from rheumatism, two admitted because of enuresis, and four with the diagnosis of epilepsy. As shown in Table I these figures compare well

TABLE I

Serum Protein Level in Healthy Subjects.

Authors.	Serum or plasma.	Number.	Age.	Average figures. Total protein.	Albumin.	Globulin.	Calculated osmotic pressure.	Sex.
Salvesen (24)	P	16	Adults	7·00	4·44	2·58	28·0	M
,, ,,		16	,,	7·02	4·35	2·68	27·7	F
Linder et alii. (15)	P	8	Adults	6·73	4·11	2·61	26·2	
Bruckman et alii. (3)	S	13	Adults	6·93	5·06	1·89	30·5	M
		8	,,	7·61	4·98	2·62	31·0	F
Moore and Van Slyke (17)	P	9	Adults	7·1	4·3	2·8	27·7	
Present series	S	20	Children	7·42	5·02	2·39	30·9	

with those obtained by workers using the same method in adults. No figures in children could be obtained for comparison. Kylin (13), using Pulfrich's refractometer to guage the serum total protein, found that in children over 2 years of age it approximated to the adult level. Serum osmotic pressure, which he measured, behaved similarly. In this series the average total protein was 7·42 grm. per cent., albumin 5·02 grm. per cent., globulin 2·39 grm. per cent., and calculated osmotic pressure 30·9 mg. Hg. The ranges were: total protein 6·78 to 8·27 grm. per cent., albumin 4·70 to 5·94 grm. per cent., globulin 1·52 to 2·94 grm. per cent., and calculated osmotic pressure 28·3 to 34·1 mg. Hg.

Groups Associated with Oedema

In Table II are shown figures obtained for serum proteins in cases of cardiac failure with oedema, nutritional oedema, the nephrotic syndrome,[2] and in acute nephritis. These groups will be discussed individually.

TABLE II

Serum Proteins in Various Types of Oedema.

	No. of cases.	Average total protein grm. %.	Average albumin grm. %.	Average globulin grm. %.	Calculated osmotic pressure mm. Hg.	Number of observations.
Normals	20	7·42	5·02	2·39	30·9	20
Cardiac failure	3	6·36	3·08	3·28	22·3	3
Nutritional oedema	2	4·11	2·76	1·35	17·1	3
Nephrotic syndrome	4	4·60	2·38	2·24	16·2	32
Acute nephritis	63	6·65	3·99	2·63	25·6	63
Level at which oedema usually occurs. Peters and others (17, 22, 29)	—	5·0	2·5	—	14–21	

A. *Oedema associated with cardiac failure.* As cardiac oedema is comparatively rare in childhood, only three cases have fallen under observation since this investigation has commenced. Payne and Peters (19) state that serum albumin is often considerably reduced in heart failure. This they attribute in the main to the accompanying anorexia and vomiting, leading to malnutrition, and therefore failure to assimilate enough nitrogen to maintain the serum proteins at the normal level. In the production of oedema in cases of circulatory failure, there appear to be three factors at work: (*a*) increased venous or hydrostatic pressure, (*b*) diminished serum albumin, and possibly (*c*) increased capillary permeability due to diminished oxygen supply to the capillary endothelium. Details of the cases are found in Table III.

TABLE III

Serum Proteins in Cardiac Oedema.

Case.	Age in yrs.	Total protein grm. %.	Albumin grm. %.	Globulin grm. %.	Osmotic pressure mm. Hg.	Oedema.	Remarks.
1	5	6·41	2·41	4·01	18·9	+ +	Rheumatic V.D.H. Pericarditis
2	4	6·71	3·79	2·91	24·9	+ +	Rheumatic V.D.H. Decompensation
3	7	5·96	3·04	2·92	23·3	+	Rheumatic V.D.H. Decompensation

From consideration of these cases it is evident that considerable reduction of serum albumin occurred, with resulting fall in osmotic pressure. In Case 1 osmotic pressure is below the oedema level, which in itself is sufficient

[2] In this paper that term is applied to patients presenting the following picture—marked oedema, albuminuria but no haematuria, absence of cardiovascular changes, no nitrogen retention in the blood and normal urea concentrating power.

to account for the oedema. In Cases 2 and 3 the reduction in osmotic pressure is not, *per se*, of sufficient degree to produce oedema. As regards the cause of the fall in serum albumin, it should be noted that Cases 1 and 2 were both wasted, and had also considerable albuminuria. On the other hand, Case 3 was well nourished and had but slight albuminuria. While Payne and Peters state that oedema may occur in cardiac failure at any level of the serum proteins, and that therefore the chief factor in its production is increased venous blood-pressure, it is obvious in these cases that diminution of serum osmotic pressure has played a part. Here both conditions laid down by Starling for oedema production—diminished osmotic pressure and increased hydrostatic pressure—were present. Perhaps the diminution of serum albumin is caused by failure in production of serum albumin, not due to deficient assimilation of nitrogen but to depression of function from circulatory failure. Although the factor of increased hydrostatic pressure is active in the production of cardiac oedema, diminution of serum protein is also frequently present and must be taken into account as a causative agent. Estimation of serum protein may therefore be of value in cases of cardiac failure with oedema, for in those cases in which the serum protein is found to be diminished, a high protein diet is indicated in order to ensure an ample supply of amino-acid for the manufacture of serum protein. In these cases, also, a 'salt-free' diet is indicated for the reason already stated that if serum osmotic pressure is diminished, the power of the serum to retain salt and water in the vessels is reduced.

B. *Nutritional oedema.* Oedema associated with famine has been recognized for many years and was prevalent in Central Europe during the war. Jansen (12) and others have pointed out that serum proteins were reduced, and the occurrence of this in patients on low protein diet. Bruckman and Peters (4) reported that oedema became manifest when serum albumin fell below 3 grm. per cent., and was seldom present when it exceeded 4 grm. per cent. In addition Bruckman and others (3) showed that oedema with low serum proteins was often present in wasting diseases such as tuberculosis, diabetes, and diarrhoea. Marriot (16) states that the oedema which occasionally occurs in coeliac disease is due to reduction in serum protein, presumably from inability to absorb nitrogen during steatorrhoea.

TABLE IV

Serum Proteins in Nutritional Oedema.

Case.	Total protein. grm. %.	Albumin grm. %.	Globulin grm. %.	Osmotic pressure mm. Hg.	Oedema.	Date.	Remarks.
1	3·76	2·85	0·91	16·9	+	16.6.31	Coeliac disease.
2	4·51	2·51	2·00	16·6	+	25.1.33	Nutritional oedema.
„	4·08	2·91	1·14	17·6	+	30.1.33	Condition unchanged. High protein diet started.
„	6·59	4·09	2·50	26·0	0	13.2.33	—

Two cases of nutritional oedema were investigated (Table IV). One was a case of coeliac disease in which oedema disappeared, with improvement in the general condition. The other case was an infant who had been fed on Nestlé's Milk for several months, but on not more than half the amount adequate for his age. The Wassermann reaction was positive.

In both cases the total serum protein, the serum albumin, and the serum osmotic pressure were low. In Case 1 globulin was also low, but unfortunately the blood of this child was not again examined after disappearance of oedema. In Case 2, following administration of a high protein diet oedema disappeared, and serum proteins were found to be almost normal, calculated serum osmotic pressure having risen from 17·6 to 26 mm. Hg. The urine in both these cases was free from albumin, and the factor leading to fall in serum protein and therefore to oedema was defective protein intake or assimilation. Whether or not the presence of congenital syphilis played any part in the production of oedema in Case 2, it is difficult to judge; but certainly oedema is not a recognized symptom in this disease. At any rate the rise of serum proteins was not due to antisyphilitic treatment, which was not instituted till after oedema had disappeared. Oedema is common in nephritis of infancy, which is thought by some to be a manifestation of syphilis in many cases. There were no signs of nephritis in this case.

C. *Nephrotic syndrome.* The figures in the group headed nephrotic syndrome in Table II are the average figures obtained during the oedematous stage in four cases. It may be said here that no case of lipoid nephrosis has occurred in the Royal Hospital for Sick Children during the past two-and-a-half years. For a diagnosis of lipoid nephrosis to be made, the rigid classification demands insidious onset, obstinate massive oedema, marked albuminuria, and no haematuria. There must be no signs of cardiovascular changes and no rise of non-protein nitrogen in the blood, and the urea concentrating power of the kidney must be unimpaired. Peters and others (22) state that a picture, clinically and biochemically indistinguishable from lipoid nephrosis, may occur in the course of glomerulo-nephritis, and that estimations of basal metabolism or blood cholesterol, which have been suggested as differentiating points, yield similar results in both types. The presence or absence of a history of acute onset with haematuria seems to be the only method of differentiation. In the four cases discussed an acute onset with haematuria was definite in three. Haematuria was observed in Case No. 2 during his stay in hospital.

In Case 1, a girl of 9 years, acute nephritis (with haematuria) developed during scarlet fever in July, 1930. Since that time she has had a history of albuminuria and of periods of oedema lasting several weeks. Admitted with oedema + +, during her stay in hospital no haematuria occurred, even microscopic. Albuminuria was marked. The urea concentration test on five occasions was within normal limits, as was the non-protein nitrogen of the blood. Blood-pressure was normal. Examination of the heart and fundi was negative.

Case 1

Date.	Total protein grm. %.	Albumin grm. %.	Globulin grm. %.	Osmotic pressure mm. Hg.	Oedema.	Remarks.
4.5.32	4·08	2·45	1·63	15·7	+ +	'Salt-free' diet started.
10.5.32	5·04	2·58	2·46	17·5	+ +	'Salt-free' high protein diet.
14.5.32	5·23	3·87	1·36	23·2	− +	
23.5.32	8·68	3·56	5·12	26·7	0	
30.5.32	5·13	3·26	1·67	20·3	0	
14.11.32	7·57	4·80	2·57	30·0	0	Out patient.
12.5.33	7·20	5·25	1·95	31·6	0	No recurrence of oedema since dismissal, 11 months previously.

Case 2 was a boy of 6 years admitted to hospital with a history of oedema of fourteen days' duration. On admission no blood, even microscopic, was found in the urine, but one week later numerous red-blood corpuscles were observed for some days. Albumin varied from one to twelve parts Esbach. Cardiovascular changes were absent. Oedema + +. At this stage the non-protein nitrogen of the blood was above normal—70 mg. per cent., but three weeks later and thereafter was within normal limits. Urea concentrating power was good throughout. On a 'salt-free' diet oedema disappeared in three weeks though the albuminuria persisted. After five weeks in hospital ordinary full diet was given, and in three days the child gained three kilos, oedema being now + +. Serum proteins, which were unfortunately only now estimated for the first time, were found to be below the oedema level. For the next four months oedema was constantly present, varying but slightly in degree, and serum proteins were always below the oedema level. The case was unfortunately lost sight of for a time, and the rise in serum protein associated with disappearance of the oedema cannot be demonstrated. However, eighteen months later the boy was seen as an out-patient. He had not relapsed since dismissal from hospital, and his urine, clear of albumin on dismissal, was still quite normal. Blood chemistry was as follows: total serum proteins 7·34 grm. per cent., albumin 4·41 grm. per cent., globulin 2·93 grm. per cent., and calculated osmotic pressure 28·4 mm. Hg., figures within the lower limit of normal as regards serum albumin and calculated osmotic pressure.

Case 3 was a girl of 9 years with a history of oedema and haematuria of four weeks' duration. On admission haematuria was microscopic only, disappearing entirely within three weeks. Cardiovascular changes were absent. Oedema + +. No nitrogen retention. Urea concentrating power of the kidneys good. Wassermann reaction negative.

This case is still under treatment. Serum proteins have been constantly below oedema level and dropsy always present.

Case 4 was a girl of 9 years who had oedema for fourteen days before admission. Blood in the urine was detected during the first week by microscope. She had no nitrogen retention, and the kidneys concentrated urea

normally. There were no cardiovascular changes. Wassermann reaction negative. Oedema + +.

Case 3

Date.	Total protein grm. %.	Albumin grm. %.	Globulin grm. %.	Osmotic pressure mm. Hg.	Oedema.	Remarks.
11.4.33	4·96	2·06	2·90	15·4	+ +	'Salt-free' diet.
17.4.33	5·09	2·18	2·91	16·1	+	Lost 2·5 kilos.
10.5.33	4·54	2·22	2·32	15·4	+	Ordinary full diet containing salt.
17.5.33	4·31	2·46	1·85	16·1	+ +	Gained 5·0 kilos. Full diet without salt.
29.5.33	4·76	2·31	2·45	16·1	+ +	Lost 2·0 kilos.

Case 4

Date.	Total protein grm. %.	Albumin grm. %.	Globulin grm. %.	Osmotic pressure mm. Hg.	Oedema.	Remarks.
28.12.32	5·07	1·71	3·36	14·1	+ +	'Salt-free' diet.
3.1.33	4·83	2·11	2·72	15·4	0	
11.1.33	4·63	2·40	2·23	16·3	0	
19.1.33	4·08	2·43	1·65	15·7	0	Full diet, containing salt.
24.1.33	4·93	2·15	2·78	15·7	+ +	Gained 4·0 kilos in 2 days.

This child also is still under treatment and still has low serum proteins and massive oedema.

From consideration of the history of these four cases it is evident that a syndrome indistinguishable from lipoid nephrosis may be a sequel to acute nephritis. Its development is rapid, within three to eight weeks of the onset in these cases. Further reference is made to cases of this type in a subsequent stage in this paper.

It is evident from a consideration of the figures obtained in Case 1 that oedema was never present when osmotic pressure exceeded 24 mm. Hg. There is an apparent anomaly in the fact that oedema was present on 14.5.32 with an osmotic pressure of 23·2 mm. Hg. and absent on 30.5.32 with an osmotic pressure of 20·3 mm. Hg. On the first date the presence of oedema must almost certainly be attributed to a lag in the excretion of fluid—only four days previously the osmotic pressure had been 17·6 mm. Hg. well below the oedema level. On 30.5.32 the osmotic pressure indicated a fall from almost normal (26·7 mm. Hg.) i. e. from a state with no oedema. During the oedema-free period diet was continued rigidly 'salt-free' so that any tendency to oedema resulting from lowering of osmotic pressure was counteracted by the absence of salt necessary to hold water.

In Case 3 the tendency to oedema was present throughout as represented by diminished osmotic pressure. But it can be seen that on a 'salt-free' diet weight was lost and oedema diminished, the opposite effect taking place when salt was added to the diet, no less than 5 kilos being gained in a few days. On salt being removed from the diet on 17.5.32 weight was again lost, although clinically no change in the degree of oedema could be

determined. Case 4 shows complete disappearance of oedema on 'salt-free' diet without marked change in serum proteins. On addition of salt to the diet 4 kilos were gained in two days without change in serum osmotic pressure.

The disappearance of oedema in Case 1 shortly after the administration of a high protein diet (the diet had previously been rendered 'salt-free') would seem to support the claims of the advocates of this form of treatment. But it must be remembered in evaluating the results of any treatment, that the nephrotic syndrome, like other diseases, often shows spontaneous remissions; these had actually occurred on several occasions in this very patient. Further caution in attributing the speedy recovery to the high protein diet must be engendered by the fact that despite the continuance of the diet the osmotic pressure fell and oedema was probably prevented merely by the absence of salt from the diet. This scepticism as to the therapeutic effect of high protein intake is strengthened by the fact that in Case 2, although the protein of the diet was always low and sometimes considerably restricted, the oedema and albuminuria disappeared in five months, and even now, a year later, no relapse has occurred. In Case 4 a high protein diet was given for four months without appreciable effect on the serum protein level. Again, as will be shown later (Table VI), those cases of acute nephritis which had moderate reduction in serum proteins were in certain instances on a low protein diet (half milk) but a return to normal occurred rapidly. It would seem, therefore, that while a rise of serum proteins may coincide with the administration of a high protein diet, this may take place even on a low protein diet. On the other hand, it appears that a salt 'free-diet' may mask the effects of low serum protein by preventing accumulation of fluid although the tendency to oedema is present.

The pathogenesis of the fall in serum albumin in the nephrotic syndrome. Although sufficient data to form conclusions on the pathogenesis of a fall in serum albumin in the nephrotic syndrome are lacking in this paper, there are grounds for the belief that the real causative factors are not malnutrition and proteinuria, as suggested by other workers. Peters and his coworkers (22) are unable to find any definite relationship between serum albumin level and proteinuria, while in the four cases described in this paper malnutrition was not present and high protein diet failed to cause a rise in the serum albumin level. For these reasons it would seem that in the nephrotic syndrome some other factor such as interference with protein synthesis must be considered.

D. *Acute nephritis.* In the group designated, acute nephritis, the average of sixty-three cases shows a reduction in total protein at the expense of the albumin fraction with a corresponding fall in serum osmotic pressure. These cases include sixteen cases in which no oedema was demonstrable clinically. (Of that number, thirteen however, lost weight during recovery so that some excess accumulation of extracellular fluid must have been present.) These

observations were made immediately on admission to hospital, that is to say, as soon as possible, and when the disease was still in the acute stage. It is evident that diminution in serum osmotic pressure is insufficient to explain the oedema. Indeed, in six cases oedema was present with normal serum proteins and osmotic pressure.

The cause of oedema in acute nephritis. In 1930, Van Slyke and others found that oedema in acute nephritis formed an exception to Starling's hypothesis in that it developed with serum proteins but slightly reduced or even at a normal level. Peters (20), discussing oedema in acute nephritis, suggests that capillary permeability is increased and that some protein escapes through the capillary wall. The result of this is a slight reduction in serum protein and the escaped protein exerts osmotic pressure in the wrong direction, i.e. tends to retain water in the extravascular spaces and acts against the osmotic pressure of the protein of the serum. As evidence of this capillary damage, he states that oedema fluids contain more protein in this disease than in lipoid nephrosis or in the nephrotic syndrome of glomerulo-nephritis. As further proof, he states that capillary haemorrhages are prone to occur in the fundi and elsewhere in acute nephritis.

I have had no opportunity of examining oedema fluids but, as Peters (21) himself admits, the difference in protein concentration in oedema fluids of acute nephritis and nephrosis is but slight. (Table V.)

TABLE V

Protein Concentration of Oedema Fluids.

Diagnosis.	Source of fluid.	Total protein grm. %.	Albumin. grm. %.	Globulin. grm. %.
Nephrotic syndrome, nephrosis	Subcutaneous oedema	0·1	—	—
,, ,, ,,	Pleural effusion	0·3–0·6	—	—
,, ,, ,,	Ascites	0·1–0·9	0·1–0·5	tr.–0·4
Acute nephritis	Subcutaneous oedema	0·1	0·1	—
,, ,,	Pleural effusion	0·6	0·5	0·1
,, ,,	Ascites	0·6–1·0	0·4–0·6	0·3–0·4

Adapted from Peters and Van Slyke.

One would imagine also that in the event of capillary damage the loss of serum protein due to escape through the damaged wall would affect both fractions. This, however, is not the case, as reduction is at the expense of the albumin fraction. It might be argued, however, that as the albumin molecule is the smaller it would escape more readily through the vessel wall, but a lesion gross enough to cause haemorrhages is unlikely to hinder the passage of globulin. It is the experience of most observers that haemorrhages in the fundi are rare in acute nephritis of children. In ophthalmoscopic examination of forty-five cases of acute nephritis in this series only one instance of capillary haemorrhage was detected, and, in this case serum proteins were normal and oedema minimal. These observations would seem to militate against the validity of the capillary damage hypothesis.

Relationship of Serum Protein to Oedema in Acute Nephritis

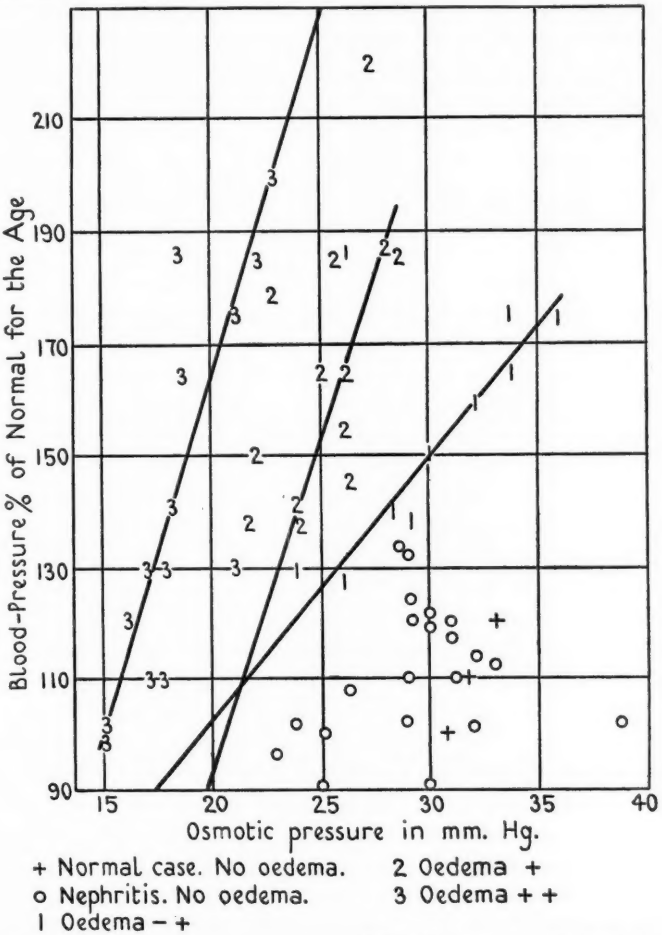
In view of the fact that the presence of capillary damage, at least as far as children are concerned, is by no means proved, an attempt has been made to determine whether any relationship exists between the degree of oedema and the serum protein level in acute nephritis. Table VI shows that there is a progressive diminution in serum proteins from almost normal in Group I (no oedema) to a fairly gross deficit in Group IV (marked oedema). The diminution in total protein is at the expense of the albumin moiety in all groups.

TABLE VI

Degree of oedema.	No of cases.	Average total protein grm. %.	Average albumin grm. %.	Average globulin grm. %.	Calculated osmotic pressure mm. Hg.
0	16	7·46	4·70	2·76	29·8
∓	14	7·06	4·25	2·79	27·2
+	19	6·37	4·08	2·30	25·5
+ +	14	5·56	2·81	2·75	19·3
Level below which oedema is usually present in nephrotic syndrome	—	5·0	2·5	—	14–21
Normal cases	20	7·42	5·02	2·39	30·9

Serum osmotic pressure reaches the critical level for oedema in Group IV only. It is thus seen that serum protein reduction cannot alone be responsible for oedema, with the possible exception of cases in which oedema is + +. Although this would seem to be an apparent exception to Starling's hypothesis, it is evident that some relation exists between oedema and the osmotic pressure exerted by the serum proteins. The maintenance of fluid balance between the blood and the tissues, however, is dependent on both the osmotic pressure of the serum proteins and the blood-pressure. In cardiac failure it has already been pointed out that increase in hydrostatic pressure occurring from increase of venous pressure is the principal factor in producing oedema, though this is accentuated by diminution in osmotic pressure. It seems feasible, therefore, that in acute nephritis both increase in capillary pressure and fall in osmotic pressure play a part in the production of oedema. In other words, a rise of blood-pressure and a fall in serum proteins occurs. Since, however, certain cases of acute nephritis show oedema with normal serum proteins and osmotic pressure, one must assume that a sudden rise in blood-pressure as occurs in acute nephritis, will by itself produce oedema. Five cases whose serum osmotic pressure lay between 30 and 35 mm. Hg. showed slight oedema with systolic blood-pressure between 150 and 180 per cent. of normal for the age. From the fact that cases of essential hypertension show no oedema unless of cardiac origin it seems that the rise of blood-pressure must be sufficiently sudden to overcome the elasticity of the tissues. It is probable that it is not so much the height of the blood-pressure that is the determining factor in the production of oedema as the rapidity with which the height is reached.

Tissue elasticity must play a part in the prevention of accumulation of extravascular fluid. The rapid rise of blood-pressure in acute nephritis will much more readily overcome the elastic resistance of the tissues than the rise which gradually occurs in chronic interstitial nephritis or essential hypertension.



The relationship of serum osmotic pressure and blood-pressure to the degree of oedema in acute nephritis.

From observation of these five cases the impression was gained that loss of oedema and fall in blood-pressure occurred together. If this conception is correct and rise in blood-pressure and fall in osmotic pressure each play a part in the production of oedema in acute nephritis then a graph should show a relation between blood-pressure, osmotic pressure, and degree of oedema. Mufson (18) who measured capillary pressure in five cases of acute nephritis found it high in all of them. Taking total serum protein

as a measure of osmotic pressure he found oedema in two of the cases where total protein was about 4 grm. per cent., but not in the others. It is interesting to note that the blood-pressure was normal or but slightly above in the three cases without oedema whose total protein varied from 5·9 to 8·1 grm. per cent. Mufson states that the blood-pressure is not a measure of the capillary pressure, and shows that there is no mathematical relation between them. In this work time has not permitted measurement of the capillary pressure, but the chart would seem to indicate the existence of relationship between blood-pressure, osmotic pressure, and oedema. In the chart the blood-pressures calculated as a percentage of normal for the age are plotted against the osmotic pressures in mm. Hg. The cases fall into four groups, those without oedema and those with various grades of oedema. From these results it would appear that changes in blood-pressure and osmotic pressure play an important part in the production of oedema in acute nephritis, at any rate as far as children are concerned, and that there is no need, and indeed no justification, for the introduction of the hypothesis of increased capillary permeability.

The pathogenesis of fall in serum proteins in acute nephritis. Epstein and many others have accounted for diminution in serum protein by loss of albumin in the urine. Peters and others (21, 22), however, in recent articles were unable to find a definite relation between serum albumin level and proteinuria, and quote a case in which serum albumin actually rose while proteinuria remained constant. On account of this they suggest that malnutrition resulting from digestive disturbances or from therapeutic restriction of protein in the diet is the important factor in causing low serum albumin in nephritis, chronic and acute.

In this series of sixty-three cases of acute nephritis nine or 14 per cent. had low serum proteins (below oedema level) with osmotic pressure below 21 mm. Hg. at the first blood examination.

Van Slyke and co-workers in twenty-three cases of acute nephritis in adults found serum proteins below the critical level for oedema in seven or 30 per cent. Table VII gives data of the nine similar cases of this series. These represent a type of acute nephritis in which a fall in serum protein produces a sufficient diminution of osmotic pressure to account for oedema. In these cases the osmotic pressure ranged from 12·8 to 20·8 mm. Hg. All had oedema + +. It is this type of case which may show the most obstinate oedema, one child having had oedema for four months and another actually for six months. In five of the cases of this series it seems hardly conceivable that proteinuria in the short space of time elapsing between the onset of the disease and the determination of the serum proteins could account for the fall in serum albumin level. If the loss of albumin in the urine per day is known it should theoretically be easy to calculate whether this is sufficient to account for the fall in serum albumin. In children, however, it is difficult to ensure collection of all the urine at the start of hospital treatment. All nine cases were well nourished, and in

none was vomiting a marked feature. As the majority of cases of acute nephritis receive whole milk in amounts sufficient to provide a quite adequate protein intake, protein restriction is not a factor. The case J.M. was actually in hospital, suffering from bronchiectasis when he developed acute nephritis. He was a well-nourished child on full diet, and prior to the onset had shown no albuminuria. Yet within two days serum albumin

TABLE VII

Cases Showing a Marked Fall in Serum Osmotic Pressure Early in the Course of Acute Nephritis.

Case.	Duration of disease at time of first blood exam.	Serum protein grm. %.			Osmotic pressure result. mm. Hg.	Result.	Duration of nephritis at time of dismissal.
		Total.	Albumin.	Globulin.			
J. M.	2 days	6·34	2·45	3·89	18·9	Well	3/12 yrs.
A. M.	5 ,,	6·31	2·92	3·39	20·8	Much imp.	6/52 ,,
C. M.	10 ,,	5·40	2·78	2·62	18·9	Much imp. (whooping cough)	3/52 ,,
C. D.	3 ,,	4·61	2·87	1·74	18·2	Well	7/52 ,,
K. L.	3 ,,	4·27	1·66	2·61	12·8	Much imp.	—
J. B.	8 ,,	4·44	3·01	1·43	18·5	Much imp.	9/52 ,,
B.McL.	30 ,,	4·96	2·06	2·90	15·4	Nephrotic syndrome	—
H. G.	14 ,,	5·08	1·71	3·37	14·1	Nephrotic syndrome	—
J. L.	5 ,,	6·25	2·51	3·74	19·0	Mixed type* of nephritis	—

* In this case serum proteins have been low and oedema present for several months. In addition marked haematuria and a considerable rise in N.P.N. of the blood have always been found.

was reduced by more than 50 per cent. In two other cases high protein diet completely failed to increase the serum protein or reduce the oedema. As far as acute nephritis is concerned it does not seem correct to claim for proteinuria or for malnutrition a place in the pathogenesis of the fall in serum proteins. It seems rather as though the mechanism of synthesis was damaged to a greater or lesser degree. In cases developing the nephrotic syndrome with protracted oedema the damage is obviously more marked than in those cases of acute nephritis whose oedema disappears as the mechanism of protein synthesis is restored, and the proteins return to normal (six out of nine cases, see Table VII). On the other hand, in hunger oedema a high protein diet causes serum proteins to rise and oedema to disappear. There is in that condition merely a deficiency in nitrogen intake below the needs of the body. In nephritis when oedema is due to low serum proteins, a high protein diet has not been found universally successful, and if malnutrition were an important factor, then, on the analogy of the foregoing, it should be equally effective in raising the level of the serum proteins. In six out of nine cases of acute nephritis, all with massive oedema associated with serum proteins below the oedema level, serum proteins rose to normal and oedema disappeared without high protein diet.

For these reasons it would seem that as in nephrosis some other factor such as interference with protein synthesis must be considered.

Value of Serum Protein Estimation in Prognosis of Acute Nephritis

Earlier in this paper it was shown (Table VI) that some relation existed between the degree of oedema and the level of serum osmotic pressure. Unless osmotic pressure falls below 21 mm. Hg., the critical level for oedema, it rises again to normal in a few weeks. It is of interest to note that fairly frequently oedema disappears before osmotic pressure returns to normal, i.e. as one would expect for reasons already stated, when the blood-pressure falls. If, however, osmotic pressure falls below the critical level prognosis must be guarded, in as much as of the nine cases of this type three have remained oedematous for long periods, serum proteins showing no indication of return to normal. In Table VII is shown the course of these cases. The remaining six pursued the customary course of acute nephritis in childhood and lost oedema rapidly, although three still had albuminuria on dismissal. By clinical examination in the first few days of an attack of acute nephritis it is not possible to foretell the outcome. In this series the estimation of serum proteins was certainly of greater value in prognosis in the early stages than non-protein nitrogen estimations or the results obtained by renal function tests. If the initial observation of serum proteins was normal it could be said with assurance that oedema would not be prolonged. Again, at no subsequent examination were serum proteins significantly below the level found at the first estimation. As far as oedema was concerned a good idea of the severity of an attack of acute nephritis was gained early by estimation of the serum proteins. Whatever the degree of dropsy if serum osmotic pressure was above 21 mm. Hg. a good prognosis could be given, if below that level a prolonged attack of nephritis with obstinate oedema might ensue as happened in 4·6 per cent. of the series of sixty-three cases.

Treatment of Oedema

It has been shown in this investigation that the oedema of acute nephritis is associated with an increase in blood-pressure and a decrease in serum protein, while in the nephrotic syndrome reduction in serum proteins with the consequent reduction in the osmotic pressure of the serum is the direct causative factor. In the majority of cases of acute nephritis oedema subsides spontaneously and a low protein diet is as effective as a diet rich in protein. Some of the cases in this series were given undiluted milk and others milk diluted with equal parts of water, but serial observations showed that in both groups any reduction of serum protein was made good in a few weeks. Even two of the six cases whose serum proteins were below the oedema level (but who did not develop the nephrotic syndrome) cleared up spontaneously on a diet of half milk. If the hypothesis, that faulty synthesis is the cause of the lowered serum protein be correct, there is no object in giving a high protein diet unless to ensure an adequate supply of

nitrogen when the ability to synthesize serum protein is restored. With the development of the nephrotic syndrome on the other hand, spontaneous cure of the oedema may be much delayed. Raised blood-pressure plays no part in its aetiology. Defective synthesis of serum protein is probably the chief causative factor, and we know of no way of remedying this. Something, however, can be done in the way of palliation by drastic reduction of the salt in the diet. When the water-holding power of the serum is diminished owing to fall in osmotic pressure the smaller the store of sodium chloride in the body the less will be the degree of oedema production. A 'salt-free' diet is indicated in any stage of nephritis, but if salt be drastically restricted there is no objection to unrestricted fluid intake.

Summary

1. The relationship of serum proteins to oedema in cardiac failure, nutritional oedema, the nephrotic syndrome, and acute nephritis in children between 2 and 13 years of age with special reference to Starling's hypothesis is studied.

2. Serum proteins have been estimated in twenty apparently normal children, in three cases of cardiac failure with oedema, in two cases of nutritional oedema (four observations), in four cases showing the nephrotic syndrome (thirty-two observations), and in sixty-three cases of acute nephritis.

(a) In cases of cardiac failure with oedema, reduction of serum albumin was found. This, in addition to increased venous pressure is thought to play a part in the production of cardiac oedema.

(b) In nutritional oedema diminution of serum osmotic pressure is directly responsible for oedema.

(c) Fall in serum osmotic pressure was a constant finding in the nephrotic syndrome but the development of oedema was in certain cases prevented by a 'salt-free' diet.

3. Evidence is given to show that oedema in acute nephritis is not due to increased capillary permeability, nor, in the majority of cases, to the fall in serum osmotic pressure *per se*, but there is evidence to show that rise in blood-pressure and fall in serum osmotic pressure may be jointly responsible for the development of oedema. The level of the serum proteins affords a valuable prognostic index: for in cases where the fall in serum osmotic pressure is not marked oedema is a very transient feature.

4. The early and gross reduction of serum osmotic pressure in certain cases of acute nephritis militates against the view that the diminution of serum proteins is entirely due to proteinuria, while the well-nourished condition of all such patients eliminates malnutrition as an important factor in the production of oedema in acute nephritis. Serum proteins may be restored to normal whether the patient is on an adequate protein diet or not. These facts suggest that defective synthesis of serum protein is the important immediate factor in reduction of serum osmotic pressure.

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CALCIFICATION OF THE KIDNEYS IN PYLORIC STENOSIS[1]

By A. M. COOKE

With Plate 39

Introduction

Among the conditions causing calcification of the kidney that of pyloric stenosis has had comparatively little attention drawn to it. The first cases were observed by Nazzari in 1896 and 1902, and were published in 1904. Both were cases of pyloric obstruction from chronic gastric ulcer with excessive vomiting and tetany. At autopsy both showed marked hyperaemia of the kidneys, the cortex of which had a granular surface and small whitish striations. In sections, these striations were seen to be deposits of a material which dissolved with effervescence in hydrochloric acid, and without effervescence in sulphuric acid, giving crystals of calcium sulphate. The calcareous infiltration was in the tubules, especially in the convoluted portion and ascending limb of the loop of Henle, and was associated with definite necrotic changes. The glomeruli appeared normal. Nazzari referred to the similarity between these changes and those well known to occur after the administrations of various poisons which act on the kidney, such as mercury, uranium, and oxalates, &c.

No further publications on this subject have been found until that of Brown, Eusterman, Hartman, and Rowntree on the renal insufficiency complicating gastric tetany. They reported eleven cases of severe renal insufficiency as a result of 'duodenal intoxication', in six of which death resulted. All the fatal cases showed on microscopical examination 'severe toxic nephritis' with granular and lipoid degeneration of the tubular epithelium and, with one exception, calcium deposits in the tubules. The authors attributed the deposits to the previous administration of calcium salts by the mouth, but remarked that Bowler (personal communication) had been unable to find any renal lesions following even excessive doses of calcium chloride. There was no evidence of pre-existing nephritis in any of the cases.

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Zeman, Friedman, and Mann examined the kidneys from four fatal cases of pyloric obstruction (two of whom had had tetany) and found in every case almost identical changes, namely, degeneration and calcification of the tubular epithelium, especially in the spiral and terminal straight portion of the first convoluted tubules. These observers interpreted the deposits as calcium on account of their heavy staining with haematoxylin and their staining by von Kossa's silver impregnation method. The resemblance between these lesions and those produced by corrosive sublimate was so marked as to cause some doubt at first as to the correctness of the clinical diagnosis. No microscopic evidence of acute or chronic inflammatory lesions was seen, and the condition was regarded as a 'toxic degenerative nephrosis'. Although three of the four cases had been given calcium salts internally, Zeman, Friedman, and Mann did not consider that this fact had any bearing on the kidney condition.

These observations were followed up by experiments on cats, in which by ligation of the pylorus similar kidney lesions were produced in eleven cases out of thirteen. The earliest changes, consisting of tubular necrosis and commencing calcification, were apparent within forty-eight hours. Grossly, the kidneys showed marked cloudy swelling and congestion, especially in the pyramids which had a characteristic violaceous tint, described by some observers in human kidneys poisoned by mercuric chloride. Microscopically, there was diffuse tubular degeneration with necrosis and calcification occurring first in the spiral and terminal straight part of the convoluted tubules, and later in the portions of tubules adjacent to the glomeruli. The blood of these animals showed the characteristic alkalotic changes of pyloric obstruction—a raised CO_2 combining power of the plasma and non-protein nitrogen, and a fall in chlorides, but no detectable change in the calcium content.

The cases reported in the present paper were collected over a period of two years, during which time the kidneys of patients dying from a variety of other diseases were examined macroscopically and microscopically, and calcification was *not* found, except in tuberculosis and in one case of poisoning by corrosive sublimate. The kidneys were obtained from the post-mortem room and at once fixed in Kaiserling's fluid, but post-mortem degeneration was always present to a certain extent, in spite of the cold chamber in which the bodies had been kept. The sections were stained with haematoxylin and eosin and by von Kossa's silver impregnation method. Attempts to stain them with alizarin as described by Cameron were unsuccessful, as is often the case with renal calcification.

In the two cases where chemical investigations were done, the methods used were as follows:

Blood was withdrawn from a vein, without stasis, into a 20 c.c. Record syringe containing 40 mg. of potassium oxalate (i.e. 2 mg. per c.c. of blood), immediately mixed and cooled under running water to room temperature. The pH of the plasma was determined at room temperature by the electro-

metric method, using the glass electrode described by Kerridge. The patient's temperature and the room temperature were noted, and the correction applied was that suggested by Havard and Kerridge, viz. 0·015 pH subtracted from the room-temperature reading for each degree centigrade of difference. The pH determinations were done within four minutes of the withdrawal of blood. Estimation of the whole blood pH in eleven normal persons by the technique described above gave readings from 7·25 to 7·40, with an average of 7·34. These figures are in accord with Millet's findings by the same method. Half of the remaining blood was then introduced, under paraffin, into a centrifuge tube and the plasma separated. The CO_2 combining power of the plasma was estimated by Van Slyke's method (1917). The urea nitrogen of the whole blood was determined by the method of Marshall and Van Slyke; the inorganic phosphorus of whole blood and of plasma by Fiske and Subbarow's method, and the chloride (as NaCl) by Van Slyke's method (1923). The urine was collected in 24-hourly specimens, preserved with toluol, the urea determined by the hypobromite method, the phosphorus (as P_2O_5) by Fiske and Subbarow's method, and the chlorides (as NaCl) by Van Slyke's method.

Case Reports

Case 1. Male, aged 43 years. This patient had a seven years' history of intermittent symptoms suggesting pre-pyloric ulcer. The symptoms had been getting steadily worse, with shorter intermissions, and for the previous three months had been almost continuous and unaffected by dieting or medicines. There had been frequent vomiting. On admission to hospital on June 30 he appeared wasted and ill. Although no visible peristalsis was seen a skiagram showed marked pyloric obstruction with tenderness of the pylorus. There was no vomiting in hospital. The urine was normal. On July 4 the abdomen was opened, pyloric obstruction due to ulcer was found and a posterior gastro-jejunostomy performed. After operation vomiting started, became worse, and by the 12th was occurring several times daily. On the 15th tetany developed and the patient was extremely dehydrated and ill. The following tables show the blood changes, treatment, and urinary changes:

Date.	pH.	Plasma CO_2 vols. %.	Urea nitrogen mg. %.	Blood NaCl mg.%.	Plasma NaCl mg.%.	
July 15	7·37	140	65	249	329	5 grm. NH_4Cl per rectum and 12·8 grm. NaCl intravenously.
,, 16	—	136	86	—	401	5 grm. NH_4Cl per rectum and 10 grm. NaCl intravenously.
,, 18	7·46	107	127	378	446	Abdomen re-opened; anastomosis satisfactory; tube tied in jejunum.
,, 22	7·17	97	114	517	632	
,, 25	Died					

Urine.

Date.	Volume in c.c.	Reaction.	Protein.	Casts.	Urea %.	Urea grm. per diem.	NaCl %.	NaCl grm. per diem.
July 16	—	Alk.	+	++	0·64	—	0·048	—
,, 17	342	,,	+	++	1·22	4·17	0·012	0·04
,, 18	690	,,	+	++	1·89	13·04	0·026	0·18
,, 19	580	Acid	+	+	2·71	15·72	0·028	0·16
,, 20	670	,,	+	+	3·16	21·17	0·028	0·19
,, 21	860	,,	+	+	3·22	27·37	0·026	0·22
,, 22	620	,,	+	++	2·88	17·86	0·033	0·20
,, 23	510	,,	+	+++	2·75	14·03	0·035	0·18
,, 24	230	,,	+	+++	2·30	5·29	0·053	0·12
,, 25	185	,,	+	+++	1·79	3·31	0·012	0·02

Post mortem. The anastomosis and jejunostomy were mechanically satisfactory; a chronic simple ulcer $1\frac{1}{4}$ inches across was found at the pylorus, and bi-lateral broncho-pneumonia was present. The kidneys ($4\frac{1}{2}$ oz. each) showed a swollen cortex with yellow streaks; the capsule was not adherent and no other naked-eye changes were seen.

[2] Sections showed:

Blood-vessels: Intimal proliferation of large vessels. No change in smaller vessels. Great engorgement with blood.

Connective tissue: Increased; fibrosis of uneven distribution. Round celled infiltration absent.

Tubules: i. Cortical group. Marked calcification. Otherwise fair preservation. ii. Loops of Henle. Calcification and degeneration present. iii. Collecting tubules. Fair preservation. In this area vascular engorgement is most marked.

Glomeruli: Bowman's capsule slightly proliferated. A few thrombosed. No gross changes.

Comment. The calcification is the exceptional feature and the sections strongly resemble experimental nephritis in rats due to uranium nitrate.

Case 2. Male, aged 28 years. The patient had a two and a half years' history of epigastric pain immediately after food and nocturnal hunger pains. He had been an in-patient eighteen months previously with the symptoms of pyloric obstruction due to ulcer. A test meal showed marked hyperchlorhydria and a barium meal pyloric obstruction. After a course of alkaline diet a second X-ray showed still a deformed duodenal cap and some degree of stenosis, but the patient was discharged free from symptoms.

He was re-admitted in February, 1932, with colicky abdominal pains and excessive vomiting of twelve days' duration. The urine contained a trace of protein. Complete pyloric obstruction was diagnosed and a laparotomy was performed. An ulcer of the first part of the duodenum was found and many adhesions; a posterior gastro-enterostomy was done. Four days after the operation, vomiting commenced and continued several times daily until death on the ninth day. The patient did not have tetany and no chemical investigations were made.

Post mortem. The stomach and proximal loop of the anastomosis were very dilated and the distal loop contracted. No mechanical cause for the obstruction could be found. The kidneys were large and pale with pro-

[2] See Plate 39.

nounced blood-streaking in the cortex. Apart from a terminal broncho-pneumonia, the other organs were normal.

Sections showed:

Blood-vessels: Normal.

Connective tissue: Not increased. No inflammatory changes.

Tubules: Extreme 'cloudy swelling'; grossly degenerate.

Glomeruli: Very much swollen. Subcapsular space obliterated.

Calcification: Widespread, especially in cortical tubules.

Comment. Subacute nephritis; suggests inorganic poison.

Case 3. Male, aged 40 years. There was a nine years' history of pyloric ulcer. Three years before he had been an in-patient and an X-ray taken then had showed some pyloric obstruction. Since being discharged from hospital he had been on a modified alkaline diet, and a year before the present admission a second X-ray had showed still pyloric stenosis with a tender duodenal cap.

He was admitted with a recent history of two weeks' abdominal pain, persistent vomiting, hiccough, and mental derangement.

Physical examination: the patient was extremely ill with cyanosis and Cheyne-Stokes breathing. Attacks of tetany were frequent and the mental state varied from delirium to actual mania. The deep reflexes were very brisk, and, as far as examination was possible, the other systems were normal. The blood-pressure was 125/108 and the urine was strongly alkaline and contained protein and acetone. The blood urea was 435 mg. per cent.

Treatment with ammonium chloride (30 grm. 'per rectum') was without avail and he died on the fourth day.

Post mortem. There were three chronic pyloric ulcers causing marked obstruction. The liver showed slight coarse cirrhosis and there was a terminal broncho-pneumonia. The kidneys were slightly smaller than normal and showed narrowing of the cortex. The capsule stripped easily and no vascular sclerosis was seen. Calcareous deposits were clearly visible to the naked eye.

Sections showed:

Blood-vessels: Enormously dilated, suggesting heart failure. Some intimal proliferation.

Connective tissue: Not grossly increased, but abnormal in amount. Areas of intense chronic inflammation (lymphocytes) especially subcapsular.

Tubules: Swollen; clear, suggest lipoid changes.

Glomeruli: Grossly abnormal. Bowman's capsule thickened. Tufts swollen and in places thrombosed.

Calcification: Widespread and very marked, particularly in cortex; corresponds roughly in distribution with the round cell infiltration.

Comment. Chronic and subacute nephritis.

Case 4. Male, aged 35 years. Five years previously this man had been an in-patient with a pyloric ulcer, confirmed by X-rays. After three years out-patient treatment he was admitted again with a recurrence and, when treated on the alkaline diet had an attack of alkalosis (this is reported as Case 8 in Reference 3). On recovering from the alkalosis and the gastric

symptoms, he remained well for two years but had then to be admitted again with a history of two months' vomiting which was becoming progressively worse. Physical examination and a barium meal showed marked pyloric obstruction. The urine was normal. While treatment by dieting and small doses of alkali was being carried out, with good clinical results, he had two considerable haematemeses on successive days. It was, therefore, decided to resort to surgery and the abdomen was opened. Gross pyloric obstruction due to scarring was found and a posterior gastro-enterostomy performed. After operation the patient started the most intractable vomiting and (in spite of a gastrostomy) died in seven days.

Post mortem. Death was due to general peritonitis. There was gross pyloric obstruction due to a chronic ulcer in the first part of the duodenum. The kidneys were small with a narrowing of the cortex and the capsule could be stripped only with difficulty, leaving a granular surface.

Sections showed:

Blood-vessels: Normal.

Connective tissue: Locally increased; i.e., in subcapsular zone. Intense subcapsular lymphocytic infiltration.

Tubules: In many cases swollen and degenerate, ? lipoid changes.

Glomeruli: Many thrombosed, others shrunken, but a great many quite normal.

Calcification: Marked beneath cortex, elsewhere slight.

Comment. Subacute nephritis.

Case 5. Male, aged 61 years. This patient had suffered from dyspepsia intermittently for ten years. The symptoms were those of duodenal ulcer, and two barium meals given while he was an in-patient six months previously had confirmed this diagnosis. After a course of alkaline diet he was discharged free from symptoms. He was re-admitted with a history of three weeks' epigastric pain, vomiting, and tarry stools.

Physical examination: the patient was pale and restless with vomiting and melaena stools. There was some arterial thickening and the blood-pressure was 150/90. The urine contained a trace of protein, and the blood urea was over 250 mg. per cent. He became steadily worse in spite of treatment, the vomiting continued, tetany appeared, and delirium with incontinence of urine and faeces supervened. Death took place seven days after admission.

Post mortem. A puckered ulcer (afterwards found to have undergone malignant change) at the pylorus was causing marked stenosis. Haemorrhage had taken place from an eroded vessel in the floor of the ulcer. The kidneys showed a swollen and congested cortex, the naked-eye appearance resembling acute nephritis. There were no changes of note in the other organs.

Sections showed:

Blood-vessels: No changes in large vessels, but engorgement of small vessels.

Connective tissue: Fibrosis and round-celled infiltration present.

Tubules: Marked calcification in the cortical group, and elsewhere widespread degeneration. Engorgement marked in collecting tubule area.

Glomeruli: Slight proliferation of Bowman's capsule. Some atrophy of glomerular tufts and a few thrombosed glomeruli.

Comment. The calcification is the exceptional feature and the sections strongly resemble experimental nephritis in animals due to uranium nitrate.

Case 6. Male, aged 58 years. In this case there was a two years' history of pyloric ulcer. One year before the present admission he had been an in-patient and an X-ray had shown pyloric obstruction, but great clinical improvement had resulted from treatment with alkalis. For six months he had not been so well, with occasional vomiting, and for a fortnight had suffered from abdominal pain and daily vomiting. On admission the patient was cachectic and dehydrated with excessive vomiting, gastric peristalsis was visible and the urine was strongly alkaline and contained a trace of protein. The cardiovascular, nervous, and respiratory systems were normal and the Sachs Georgi reaction negative. There were no signs of tetany. He was treated by dieting and powders of tri-calcium phosphate, but the vomiting continued unabated. Alkali was then stopped and 20 grm. of sodium chloride given intravenously in two doses. Temporary improvement followed, but, on account of his inability to retain fluid by stomach or rectum, a jejunostomy was done, and for the alkalosis, which had become worse, 20 grm. of ammonium chloride was given by the jejunostomy during two days. The effect of the latter treatment was to give the patient a severe acidosis. An attempt was made to correct this by the administration of sodium bicarbonate, but the patient died eight days after the jejunostomy.

Blood.

Date.	pH.	Plasma CO_2 vols. %.	Urea nitrogen mg. %.	Blood NaCl mg. %.	Plasma NaCl mg. %.	Plasma phosphate mg. %.
April 22	—	—	138	359	—	—
,, 24	7·42	113	133	474	552	—
,, 26	7·38	98	126	529	625	—
,, 29*	7·50	99	90	504	601	—
May 2	7·32	41	90	642	714	—
,, 5	7·08	30	108	682	725	—
,, 6	7·18	37	118	629	714	7·1
,, 7	7·21	37	137	617	686	—
,, 8	Died					

* Between April 29 and May 2 20 grm. of NH_4Cl were given

Urine.

Date.	Volume in c.c.	Reaction.	Protein.	Casts.	Urea %.	Urea grm. per diem.	NaCl %.	NaCl grm. per diem.	Phosphorus %.	P_2O_5 grm. per diem.
Apr. 25	Cas. spec.	Alk.	+	+	1·79	—	0·19	—	0·033	—
,, 27	1540	Alk.	+	0	1·65	25·41	0·19	2·93	0·029	2·04
,, 28	1410	Alk.	+	Few	1·95	27·49	0·20	2·82	0·046	2·97
,, 29	1210	Alk.	+	—	2·08	25·17	0·18	2·18	0·054	3·0
,, 30	Cas. spec.	Neut.	+	0	1·6	—	0·14	—	0·062	—
May 1	870	Acid	+	++	2·2	19·14	0·14	1·22	0·048	1·91
,, 2	1910	Acid	Trace	+++	2·07	39·54	0·18	3·44	0·050	4·37
,, 3	1600	Acid	Trace	+++	1·88	30·08	0·28	4·48	0·066	4·85
,, 4	Cas. spec.	Alk.	Trace	+++	1·94	—	0·10	—	—	—
,, 5	Cas. spec.	Acid	Trace	++	1·67	—	0·08	—	—	—
,, 6	Cas. spec.	Acid	+	++	1·65	—	0·12	—	0·063	—
,, 7	No specimen—incontinent									
,, 8	Died									

Post mortem: A large chronic ulcer, just on the stomach side of the pylorus, was causing marked stenosis. There was a terminal bronchopneumonia, but no gross pathological changes in the other organs, except the kidneys. These latter were of normal size, with slight narrowing of the cortex, appeared much paler than normal, and showed a few recent haemorrhages. The capsule stripped easily.

Sections showed:

Blood-vessels: Intimal proliferation of large vessels and engorgement of small vessels.

Connective tissue: Some fibrosis, but no round-celled infiltration.

Tubules: Calcification present in the cortical group. Elsewhere, widespread degeneration.

Glomeruli: Nil.

Comment. The calcification is the exceptional feature and the sections strongly resemble experimental nephritis in animals due to uranium nitrate.

Discussion

The cases were clinically very similar in character, all having chronic gastric ulcer or carcinoma followed by pyloric obstruction and vomiting which had lasted for from twelve to thirty days. Three had tetany, and in the two cases where chemical investigations were done, a severe alkalosis was present. With one exception, the urine contained protein at some stage of the illness. A similar close correspondence between the post-mortem findings is also apparent; in all cases gross pyloric obstruction was present and the kidneys were abnormal to naked eye and microscopic examination. The reports on the sections, for which I have to thank my colleague, Dr. R. J. V. Pulvertaft, may be summarized as follows: The blood-vessels, connective tissue, and glomeruli showed little change, except for the degenerations of age in the older patients; the tubules, however, were the seat of gross degeneration, lipoid changes and calcification in every case. According to Wells, the chief factors in the chemistry of dystrophic calcification are:

(1) The amount and state of the blood calcium. No calcium estimations were done in any of these cases, but practically all authors [2] who have investigated this point are agreed that there is no appreciable deviation from the normal (in the total calcium at any rate), so that hypercalcaemia does not appear to be a factor as it is in metastatic calcification.

Furthermore, no published accounts have been found where excessive calcium feeding has, by itself, caused pathological calcification.

(2) Retrogressive changes are essential; hyaline degeneration and necrosis being especially favourable. Both were present in the series under discussion.

(3) Slowing of the circulation. The congestion found in the sections suggests that this was present.

[2] See references 1, 9, 10, and 15.

(4) The formation by degeneration of substances with special affinities for calcium salts. Lipoid bodies which could provide materials for the calcium soaps commonly supposed to precede the deposition of calcium phosphate (which is the invariable composition of the deposits) were present, as far as could be ascertained by ordinary microscopic examination.

(5) Physical conditions favouring the local absorption of salts, the least soluble of which accumulate in excess. The increase in inorganic phosphorus in the blood is one of these conditions.

(6) Increased alkalinity of the blood and tissues. This factor was also present, and was probably accentuated by the increased alkalinity of dead and dying tissues (Kleinmann).

It will thus be seen that the chemical state of the blood, urine, and presumably of the tissues, in the alkalosis of pyloric obstruction is peculiarly favourable to dystrophic calcification of the renal epithelium.

As might be expected these changes in kidney structure are associated with considerable changes in function, and several writers have drawn attention to the renal insufficiency which complicates pyloric and high intestinal obstruction. In 1914, Tileston and Comfort described the rise in non-protein nitrogen which occurs in high obstruction, and, in fact, in any case of sufficiently severe vomiting, and noted the common occurrence of proteinuria. Five years later McQuarrie and Whipple made a fuller study and proved that there was an actual failure of the kidney to concentrate. In 1922, Tucker reported eight cases of 'uraemia' following gastro-enterostomy, and these observations have been confirmed in the paper of Brown, Eusterman, Hartman, and Rowntree referred to in detail above. Animal experiments by Hartwell, Hoguet, and Beekman have given parallel results. In my cases a similar picture is found, as reference to the figures in the cases where chemical analyses were done will show. In Case 1, for example, it will be seen that on the day of death there was extreme oliguria and cylindruria and a urea concentration of only 1·79 per cent. with a blood urea of 244 mg. per cent. This gives a urea concentration factor of 7·3 which indicates, of course, grave renal insufficiency. Again, in Case 6, there was 1·65 per cent. of urea in the urine and a blood urea of 294 mg. per cent., the urea concentration factor being even lower, namely 5·6.

In a previous communication a series of cases has been reported where temporary renal insufficiency was associated with the alkalosis which sometimes occurs following the administration of alkalis to patients in the treatment of gastric and duodenal ulcers. The clinical picture presented by these patients and the results of chemical investigation closely resemble the findings in the present series, except that in the latter the alkalosis is more severe and the renal insufficiency greater.

Numerous hypotheses have been put forward to account for the toxaemia and general metabolic changes found in pyloric obstruction, and factors which are widely accepted at the present time as being the cause are hypochloraemia and alkalosis. With regard to the former, chloride loss

by itself does not appear to affect the kidneys adversely, or at any rate to raise the blood urea. For example, in the hypochloraemia sometimes met with in burns when there is a large amount of chloride lost in the serous exudate, there is no rise in the blood urea (Underhill, Carrington, Kapsinow, and Pack).

In view of this and of the closely parallel nature of the clinical and chemical findings in the cases of alkalosis from alkali excess and from acid loss, it is suggested that the renal changes—functional and structural—found in pyloric stenosis are due to the alkalosis which is present.

Summary

Six fatal cases of pyloric stenosis with excessive vomiting are described in which characteristic renal changes were found after death.

It is suggested that the renal changes were due to the alkalosis which was present.

My thanks are due to the Staff of St. Thomas's Hospital for permission to publish these cases.

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Fig. 1.—Section of kidney from Case 1, stained with haematoxylin and eosin.

Fig. 2.—Another section from the same Case, stained by von Kossa's silver impregnation method and counter-stained with safranin.

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PITUITARY SECRETION IN HIGH BLOOD-PRESSURE[1]

By CLIFFORD HOYLE
(From the London Hospital)

With Plates 40 to 44

THE pituitary and adrenal glands are the only organs known to secrete a substance which raises blood-pressure. It might be expected that excessive secretion from either gland would lead to hypertension. This question has often been raised for the adrenals, but trustworthy evidence has not yet been produced to show that high blood-pressure is ever due to hyperadrenalinism, though this is a likely explanation in the rare instances of adrenal paraganglioma (3), (12), (28), (29), (31), (32). On the other hand, pituitary function in high blood-pressure has scarcely been mentioned, and certainly had not been investigated until the recent research of Hoffman and Anselmino (2), (19), who suggested that 'hyperpostpituitarism' may be the cause of eclampsia with hypertension. They found in blood ultrafiltrates from eclamptic patients an excess of a principle which raised blood-pressure and inhibited diuresis. It had certain chemical properties also like those of pituitrin.

The present investigations began some three years before that work was published, and they have been concerned only with pituitary function in essential hypertension and in hypertension accompanied by chronic renal insufficiency. Cerebrospinal fluid was examined for pressor, melanophore-expanding, and oxytocic activity. It was chosen because previous investigations on pituitary secretion seemed to show that it is the route by which the active principles of the posterior lobe of the gland are discharged.

Herring (16) was the first to suggest that the posterior lobe secretes directly into the cerebrospinal fluid. Since then discussion has turned mainly upon whether the active principles can be detected in the fluid. Cushing and Goetsch (9) found that concentrated human cerebrospinal fluid produced a pressor response when injected into experimental animals, and also dilated the frog's pupil and contracted the bladder, uterus, and intestines. They concluded that the active principle was most probably pituitrin, and they anticipated the possibility of determining the functional activity of the posterior lobe by such tests. Carlson and Martin (7), however, objected to these conclusions because the fluids tested were pathological and were concentrated twenty to thirty times by evaporation on a water bath. These observers were unable to detect in normal unconcentrated cerebrospinal

[1] Received July 10, 1933.

fluid from dogs any pressor substance or any substance which affected sugar tolerance. They used as much as 50–100 c.c. for each test. Wassing (48), similarly failed to detect pituitrin in cerebrospinal fluid, and Cow (8) found that normal cerebrospinal fluid from dogs contains pituitary secretion only in minute amounts. To produce any effect on the uterus of the guinea-pig, which is the most sensitive test organ, two to three c.c. of normal cerebrospinal fluid were required in a bath of 80 c.c. of Ringer's solution; but after injections of an extract of duodenal mucous membrane as little as ten minims then produced a well marked contraction, and dilated the pupil of the enucleated eyeball of the frog, and constricted the blood-vessels of the frog. Larger amounts, upon intravenous injection, led to a slight but typical rise of blood-pressure in cats with an accompanying diuresis, and also produced a marked increase in mammary secretion in the lactating cat. Like pituitrin, the active principle in the cerebrospinal fluid was soluble in water but insoluble in absolute alcohol and ether, and was inactivated by tryptic digestion. Oehme (41) obtained strong vasoconstriction in the vessels of the rabbit's ear by perfusing cerebrospinal fluid. In 1920 Jacobson (23) reinvestigated the problem and found that moderate concentration of human and bovine cerebrospinal fluid have a slight depressor effect followed by a more or less prolonged pressor effect when injected intravenously. The former was similar to the fall in blood-pressure which follows injection of various tissue extracts, and most probably was due to histamine. The pressor effect was always slight and was attributed to the volume of fluid injected or to over-reaction to the depressor effect, and not to the presence of posterior lobe secretion. Herring (17) also, using Ringer extracts of dried cerebrospinal fluid, found no appreciable amount of pituitrin in fluid taken from the fourth ventricle of cats.

These contradictory results have since been followed by many observations which show that in animals the secretion passes directly into the cerebrospinal fluid where it may be detected under suitable conditions. Dixon (10) showed that the cerebrospinal fluid of dogs contained an oxytocic substance which has every known chemical and physiological action of pituitrin. He found that the amount varied normally, but that the secretion was not affected by any form of nerve stimulation, by the inhalation of oxygen, carbon dioxide, or chloroform, or by administration of alcohol, urea, caffeine, histamine, adrenalin, or 'β' telluronium dichloride, or by extracts of numerous tissues. Trendelenberg (45), (46), and Miura (38), confirmed this, and proved that an oxytocic substance cannot be detected after the pituitary gland has been removed or its stalk occluded. McLean (36) found that fresh human cisternal and ventricular fluid contained from 25μ mg. to 240μ mg. (five specimens) when obtained without general anaesthesia: ventricular fluid from etherized patients was inactive. Canine cerebrospinal fluid in 50 per cent. concentration had a considerable effect in darkening frog melanophores and also a corresponding oxytocic action. Geesink and Koster (14), also have demonstrated the presence of considerable amounts of oxytocic substance in canine cerebrospinal fluid. Karplus and Plczenik (25), have recently shown that electrical stimulation of the tuber cinereum in animals increases the amount of oxytocic and melanophore-expanding substances present in the fluid. This is strong evidence that these active pituitary principles are discharged partly, if not entirely, into the ventricular fluid.

Dixon (10) showed that extracts from the interstitial tissue of the ovary have a specific effect in exciting secretion by the posterior lobe of the pituitary. Dixon and Marshall (11) found that extracts from ovaries con-

taining corpora lutea, whether of pregnancy or oestrus, had no effect upon pituitary secretion so long as the corpora lutea remained fully active. During involution of the corpora lutea the power of extracts from the interstitial tissue of the ovary to stimulate the pituitary became progressively greater. Dixon and Marshall suggested that physiological parturition is induced by the cumulative effect of increased activity of the pars intermedia of the gland brought about by the action of an ovarian hormone which is only produced in the absence of fully formed corpora lutea. It has since been shown that labour may be induced in pregnant women near term by the injection of cerebrospinal fluid from parturient patients (34). Heller and Holtz (15), have recently confirmed Dixon and Marshall's theory, and have also shown that the uterus probably becomes more sensitive to pituitrin at term.

Dixon and Marshall's results have met with certain criticism. Blau and Hancher (4) found that the oxytocic activity of cerebrospinal fluid in animals was increased by injections of histamine and also by extracts of a number of tissues, e.g. testis, liver, and spleen, as well as the interstitial tissue of the ovary. They concluded therefore, that the effect of ovarian extracts was not specific. Also Van Dyke and Kraft (47), found that the oxytocic activity of cerebrospinal fluid from women during the latter part of pregnancy or during labour was no greater than that of normal controls. These contradictory results are not yet reconciled, but the source of cerebrospinal fluid used for such tests is a crucial point. Dixon himself failed to find an oxytocic substance in canine cerebrospinal fluid taken by lumbar puncture, and he attributed this to absorption of the active principle from the subarachnoid space. There is now good evidence that lumbar fluid contains considerably less oxytocic principle than fluid taken from the cisterns; often none can be detected in the former. Trendelenberg (45), and Miura (38), found this to be so in dogs, and McLean (36), Jánossy and Horváth (24), and Mestrezat and Van Caulaert (37) met the same difference in man. It must now be recognized that pituitrin is normally rapidly absorbed into the circulation after secretion into the cerebrospinal fluid, and that little or none reaches the lumbar region of the cord.

The activity of the posterior lobe of the pituitary has also been investigated recently in epilepsy and under the influence of diuretics. Altenburger and Stern (1). found that the oxytocic activity of human cerebrospinal fluid is often reduced in epilepsy, especially during the fits. They suggest that the posterior lobe secretion may be concerned with inhibiting the seizures. Hoff and Wermer (18), have shown that certain diuretic drugs, such as euphyllin, novasurol, and urea, increase the oxytocic hormone present in cerebrospinal fluid. They suggested that diuresis leads to dehydration which in turn is the stimulus to increased pituitary secretion. Although considerable amounts of pituitrin were found in cisternal cerebrospinal fluid from patients with diabetes insipidus, there was no increase after administering euphyllin. They believe that this is due to injury which interferes with the innervation of the gland. The same investigators also found that excitement led to a considerable increase in the pituitrin present in the cisternal fluid of dogs. They related this to the inhibition of diuresis which excitement produces; small doses of such hypnotics as luminal or trichlorisobutyl alcohol prevented both the increased secretion of pituitrin and the inhibition of diuresis.

The concentration of oxytocic substance which has been found in cerebrospinal fluid has varied widely with different observers. In the normal dog Dixon (10), concluded that as much as 6 to 60×10^{-2} mg. per c.c. of standard fresh *pars posterior* may be present. Trendelenberg (45) and Miura (38),

found only 3 to 4×10^{-4} mg. per c.c., and Van Dyke and Kraft (47), found similar amounts in human cerebrospinal fluid taken by lumbar puncture and in canine cerebrospinal fluid taken by cistern puncture. Their recorded figures vary from 2×10^{-4} mg. per c.c. to 20×10^{-4} mg. per c.c.

This review of the literature shows that the factors which may affect the secretion of pituitrin are still imperfectly understood, and we have scarcely any knowledge of how the secretion may be affected in disease.

Methods

The experimental methods used for the detection of pituitrin are now well established, but so far as body fluids are concerned they have been applied almost solely to its recognition in cerebrospinal fluid in order to avoid the technical difficulties introduced by using blood filtrates. It was this consideration which decided the choice of cerebrospinal fluid for the tests in the present investigations. The fluid was obtained by lumbar puncture with a Greenfield needle. The pressure was determined with a manometer, and a Queckenstedt test was made to ensure that the lumbar fluid was in free communication with the cerebral cisterns. The fluid was then collected slowly into clean sterile test-tubes, as three or four successive samples of 5 to 10 c.c. each. These were tested separately so as to avoid the difficulty of testing only fluid lying within the lower spinal theca. As there is probably about 100 to 150 c.c. (42) of cerebrospinal fluid in the human adult, removal of 30 c.c. to 40 c.c. would mean that the latter part came from the basal cisterns and so would be identical with fluid obtained by cisternal puncture. The first sample was used for routine estimation of cells and protein and for a Wassermann reaction. All the experimental tests were made as soon as possible, but the fluid was stored in an ice-chest in the meantime.

As the amount of cerebrospinal fluid available from each patient was limited, a choice had to be made between the various tests for detecting posterior lobe secretion. Tests for pressor activity were made in all but three patients as the investigations were concerned with the pressor function of the gland. Melanophore-expanding and oxytocic activity were also determined whenever sufficient fluid was available. Pressor activity was determined in cats, or occasionally in rabbits. In most of the experiments the animal was pithed in order to secure a low blood-pressure giving maximum sensitiveness to pressor substances. Usually a basal blood-pressure of about 60 mm. Hg. was obtained ; this is the most sensitive level. The anaesthetized animal is less sensitive than one which has been pithed, but occasionally urethane anaesthesia was employed and then both vagi were cut in the neck. Artificial respiration was maintained with a Brodie's pump. The arterial blood-pressure was measured from one carotid artery connected to a writing mercury manometer by a cannula in the usual way. In many of the experiments intestinal vascular volume was also recorded. The cerebrospinal fluid was injected intravenously into the jugular or femoral veins. Control injec-

tions of saline, Ringer's solution, and of standarized posterior lobe extract ('Pitressin') were made in order to judge individual susceptibility to the volume effects of intravenous injections and also to the pressor substance of the posterior pituitary lobe. Variations in both these factors must be considered when interpreting the experimental results.

The determination of melanophore-expanding activity was made upon frogs (*R. temporaria*) by the method described by Hogben and Winton (21). Frogs of about 18 to 20 grm. were kept exposed to daylight at a temperature of 20°C. to 24°C. in a dry glass tank with a white floor for a few days before use. When required they were matched in pairs of identical colour and kept in suitable dry glass jars on a white background in sunlight for a few hours. Any that were not sufficiently pale in colour or were not exactly matched were then rejected. One member of each pair was injected intraperitoneally with cerebrospinal fluid or a standard pituitrin solution, the other with saline or Ringer's solution as a control. The results of the tests were taken one and a half hours after the injections, as Hogben and Winton (21) have shown that expansion of melanophores due to posterior lobe extracts only lasts for one and three-quarter to two and a half hours when minimal doses are used. Naked eye comparison of the colour of the control and experimental frogs was checked by microscopic determination of the extent of melanophore-expansion in the web of the foot.

The oxytocic activity of the cerebrospinal fluids was determined by the usual technique employed for the standardization of posterior lobe (pituitary) extracts. This is a modification of that introduced by Dale and Laidlaw and later improved by Burn and Dale (5) and others. Especial care was taken to ensure that the virgin guinea pigs had been separated from males soon after weaning, and that they weighed between 170 and 270 grm. It was ascertained that oestral activity was absent, and during dissection the uterine horn was handled with the greatest care. Water distilled and condensed in glass, and analytical chemicals were used for making up the modified Ringer-Locke solution (6), and the temperature of the oxygenated bath was kept constant at 37°C.

Specificity and sensitiveness of the tests. Only the melanophore-expanding reaction of the three tests used can be regarded as 'specific' for posterior lobe secretion. The oxytoxic action is so remarkably sensitive however—approximately a minimum effective concentration of one in 1,000,000,000 may sometimes be recognized—that it is in this sense practically a specific test when used for the detection of minute concentrations. Melanophore-expansion is abundantly proved to be a special function of posterior lobe secretion (21), (22): no other tissue extract has a similar action (22), and although nicotine, apocodeine, and digitalis effect a partial expansion (22) they do so only in doses nearly lethal. Histamine has no effect on melanophore-expansion; adrenalin, tyramine, and ergotoxine produce contraction (22). Di Mattei has recently claimed that certain glandular extracts will cause expansion of melanophores (33), and that chloretone tends to interfere with

the reaction. His former claim is not confirmed by others, and investigations made in connexion with the present work failed to show that chloretone has any influence upon melanophore-expansion.

The sensitiveness of these various tests is obviously important when they are to be used for obtaining evidence upon pituitary secretion. In the present investigation this is immediately related to the amount of cerebrospinal fluid that should be used for each test in order to demonstrate with certainty the presence or absence of active principles in amounts which might effect an action in the body. Yet although a vast amount of study has been given to the assay of pituitary extracts, much more evidence upon the sensitiveness of the methods used is still needed.

The oxytocic and melanophore reactions are more sensitive than the pressor test and are trustworthy, though the permissible range of error is about ± 10 per cent. (40). McCord (35) reported the minimum effective concentration of pituitary preparations to be 1 in 1,000 millions with the oxytocic test, but Trendelenberg (45) found that one part of fresh gland in 20 millions (50μ mg. per litre) was the threshold. Lampe (30) tested a series of extracts made from twenty human pituitary glands dehydrated with acetone. The minimum effective concentrations ranged from 1 in 12 millions to 1 in 700 millions. The oxytocic and antidiuretic results agreed but differed from the pressor assays. Burn and Dale (5) made no comment upon the sensitiveness of the test.

Fenn (13) produced expansion of melanophores in frogs with a dilution of one part of fresh gland in 10^{10} parts of solution. Hogben and Winton (21) showed that the test is sensitive to 0·00019 c.c of 'infundin' (Burroughs Wellcome & Co.) equivalent to 5×10^{-5} grm. of fresh ox gland. They found that the mean deviation was 12 per cent. when four to eight frogs were used for each standardization. Krogh (27) finds that the general colour of the frog's leg to the naked eye is the best index, and that the test is sensitive to one part of dried pituitary powder in 200,000,000 or 0·005 mg. per litre, with an error of 15 per cent.

The pressor test is much less sensitive than the oxytocic or melanophore tests, though the minimum effective concentration seems to have received no comment in the literature (6), (20), (40), (43), (44). Krogh (26), however, noted that frog capillaries contract with a dilution of 1 in 500,000 of a commercial pituitary extract. This concentration did not affect arteries. Swanson (44) used doses of 0·1 to 0·5 unit for standardizations, and he pointed out that cats anaesthetized by amytal or other basal anaesthetics were as sensitive as decerebrate animals and gave equally trustworthy results. Both with decerebrate and anaesthetized cats the error of standardization is about 10 per cent.

Results

1. *Controls.* Cerebrospinal fluids from seventeen control patients were investigated. The fluids were tested for pressor activity in sixteen, for melanophore-expanding activity in seven, and for oxytocic activity in five. The controls comprised three patients with diabetes mellitus, two with disseminated sclerosis, one with multiple peripheral neuritis, one with chronic encephalitic Parkinsonism, one with traumatic Parkinsonism, one

with syphilitic meningitis, one with tuberculous meningitis, one with meningococcal meningitis, one with hysteria, one with obstructive jaundice due to gallstones, one with supposed carcinoma of lung, one with a chronic duodenal ulcer, one with simple tachycardia, and one with severe pyorrhoea. Their ages ranged from 9 to 58 years and 10 were over 30 years of age. In all of them the cardiovascular system was normal.

All the results obtained with the three tests in these control patients were negative. As much as 30–40 c.c. of cerebrospinal fluid was usually taken in three or four successive samples which were tested independently. Plate 40, Fig. 2, illustrates a typical result; it shows the effect of two injections of successive samples of cerebrospinal fluid from a control patient (chronic duodenal ulcer) on the blood-pressure and intestinal vascular volume of a pithed cat. Another example is illustrated in Plate 43, Fig. 9. A typical result of the tests for oxytocic activity is shown in Plate 41, Fig. 4 (1): The small spontaneous contractions of the guinea-pig's uterus were unaffected by adding to the bath cerebrospinal fluid from a control patient with disseminated sclerosis. These results show that usually the posterior lobe secretion cannot be detected in fresh unconcentrated human cerebrospinal fluid even when the fluid drawn by lumbar puncture has been sufficient to ensure that the sample tested came from the cerebral cisterns.

2. *Essential hypertension.* Twenty-six cases of essential hypertension were investigated. Their ages ranged from 23 to 75 years, and the duration of symptoms varied from a minimum of two weeks up to 6 years. In every patient the systemic blood-pressure in the brachial arteries had been recorded on many separate occasions and, except in one patient, had been known to be consistently raised for a period of not less than several months. The lowest systolic pressure was 185 mm. Hg. except in eight patients who had heart failure. In these the lowest systolic pressure was 145 mm. Hg. The highest systolic pressure observed was 240 mm. Hg. The lowest diastolic pressure was 100 mm. Hg. except in five patients who had heart failure. In one of these who had recently had a thrombosis of a coronary vessel it was as low as 65 mm. Hg. The highest diastolic pressure was 150 mm. Hg. In all except two there was radiographic or clinical evidence of enlargement of the heart and other accompanying evidence of cardiovascular hypertrophy. The Wassermann reaction in the blood-serum or cerebrospinal fluid was positive in one patient only. Renal function was determined by estimating the blood urea, the urinary excretion of phenolsulphonephthalein and the standard clearance of urea by the Van Slyke method (39), and was normal in all except two patients in whom severe congestive heart failure was present. The cell content of the cerebrospinal fluid was always normal and with three exceptions the protein content was never greater than 0·05 per cent. The cerebrospinal fluid from all 26 patients was tested for pressor activity; in 16 it was also tested for melanophore-expanding activity, and in 15 for oxytocic activity.

Only occasionally did the tests afford evidence of the presence of unusual

amounts of posterior lobe secretion in the cerebrospinal fluid. Almost always, as in the controls, intravenous injection of cerebrospinal fluid had no effect upon the blood-pressure in the pithed cat, and when the intestinal vascular volume was recorded this also failed to show evidence of any vasoconstriction. Sometimes a small volume effect due to the bulk of fluid injected was to be seen on the tracings, and this was controlled by noting the effect of saline or Ringer's solution. Plate 40, Fig. 1, shows a typical record in which this volume effect was evident and was no greater than the slight change after injecting an equal amount of saline: in neither case was there any alteration in the intestinal vascular volume.

Pituitary secretion was never detected in the second sample, which presumably contained more cerebrospinal fluid from around the brain-stem, when the first sample failed to show its presence. Plate 40, Fig 2, illustrates such an experiment in which two successive samples of cerebrospinal fluid from a hyperpietic patient were compared with two similar samples from a patient with a chronic duodenal ulcer who had a normal blood-pressure. Neither of the two samples from either patient had any effect upon the blood-pressure or the intestinal vascular volume in the experimental animal. A typical result of the melanophore test is shown in Plate 41, Fig. 3, where the negative effect of injecting 3 c.c. of cerebrospinal fluid from a patient with hypertension is compared with the positive effects of 1/40 and 1/20 unit of 'Pitressin'. A typical result of the oxytocic tests is shown in Plate 41, Fig. 4. Neither control cerebrospinal fluid nor that from two patients with hypertension had any effect upon uterine movements; pituitary extract (Pitocin) produced a marked contraction.

Occasionally, it was thought that a cerebrospinal fluid produced a rise of blood-pressure greater than could be attributed to any volume effect, and in 3 out of the 26 patients this was quite definite. In each of these the rise was shown to be due to the presence of an unusual amount of posterior pituitary secretion because the fluid also gave a positive reaction to the melanophore test. Plate 41, Fig. 5, and Plate 42, Fig. 6, show the rise of blood-pressure in a pithed cat which followed injection of cerebrospinal fluid from two of these patients. In Plate 41, Fig. 5, the effect of injecting cerebrospinal fluid from one of these patients is compared with the effect of saline and also of a standardized posterior lobe extract. 3 c.c. of the cerebrospinal fluid had a rather less pressor effect than 1/250th of an international unit of 'Pitressin'. In Plate 42, Fig. 6, the effect of cerebrospinal fluid from another patient is shown to be rather greater than this. Several samples taken had an equal action, which shows that the distribution of the pressor substance was fairly uniform throughout the fluid. Both samples gave a positive result with the melanophore test (Plate 42, Fig. 7).

Thirteen out of the fifteen fluids that were tested for oxytocic activity yielded completely negative results, one gave a weak positive reaction and one only a decided positive reaction. The latter was obtained with a cerebrospinal fluid which also had a pressor effect in the pithed cat.

Eight of the hyperpietic patients included in this group had evidence of congestive cardiac failure at the time the cerebrospinal fluid was taken for investigation. As anoxaemia may increase the secretion of pituitrin it might be thought that cardiac failure would sometimes lead to an excess in the cerebrospinal fluid. No evidence of this was obtained. Plate 43, Fig. 8, shows a typical tracing where the effect upon the blood-pressure of a pithed cat of injecting 4 c.c. of cerebrospinal fluid from a patient with severe heart failure is compared with the effects of Ringer's solution and with 1/10th of an international unit of 'Pitressin'. This patient's cerebrospinal fluid also gave a negative result with the melanophore test.

3. *Hypertension accompanied by chronic renal insufficiency.* Sixteen patients were investigated in whom high blood-pressure was accompanied by chronic renal insufficiency affecting nitrogenous excretion. In ten the renal failure was thought to be consecutive to essential hypertension. In the remaining six nephritic changes were probably primary, though in one only, a woman of forty-four, did the symptoms date from a recognized attack of acute nephritis. In the other five the renal changes had been insidious (nephritis repens) and in one they had been preceded by cystinuria with renal calculus. The former group were all middle-aged or elderly patients; their ages ranged from 49 to 71 years, and the duration of symptoms from 10 days to 5 years. In the latter group the ages ranged from 9 to 44 years, and the duration of symptoms from 2 months to 10 years. With one exception the systolic blood-pressure was consistently raised during observation in all the patients in each group. The lowest systolic pressure recorded in any patient was 140 mm. Hg., and the highest was 295 mm. Hg.; the lowest diastolic pressure was 85 mm. Hg., and the highest was 210 mm. Hg. In all the patients save one there was clinical or radiographic evidence of enlargement of the heart and other evidence of cardiovascular hypertrophy. In every patient the Wassermann reaction in the blood-serum or cerebrospinal fluid was negative; the cell and protein content of the cerebrospinal fluid was normal, except in one patient in whom the latter was raised to 0·11 per cent. All the patients showed impairment of renal function at the time the investigations were made. The blood urea was abnormally raised in eleven, with a maximum of 88 mg. per cent. In eleven the excretion of phenol-sulphonephthalein was defective, with a minimum excretion of only 9·65 per cent. in two hours: in twelve the standard clearance of urea was abnormally reduced.

The cerebrospinal fluids of fourteen out of the sixteen patients were tested for the presence of pressor bodies. In four they were also tested for melanophore-expanding activity, and in six for oxytocic activity. In every case these tests gave negative results. Plate 43, Fig. 9, shows a typical tracing where the effects of injecting cerebrospinal fluid from a patient with high blood-pressure and chronic renal failure, and from a control patient are compared upon the blood-pressure and intestinal vascular volume of a pithed cat. In both cases there is a complete absence of any pressor response. The

hyperpietic patient in this instance had severe paroxysmal dyspnoea when the cerebrospinal fluid was taken. Plate 44, Fig. 10, shows a similar negative result obtained with a patient aged 44, who had a long-standing chronic azotaemic nephritis following upon acute nephritis in adolescence. Although she had few symptoms at the time of these investigations, she had marked cardiovascular hypertrophy with a brachial blood-pressure of 170/105 mm. Hg. and a blood urea of 88 mg. per cent.

Two or more samples of cerebrospinal fluid were usually taken successively and tested separately, but a pressor substance was never detected in a later sample. Plate 44, Fig. 11, illustrates this in the case of a patient, aged 26, who had a chronic nephritis (nephritis repens) with a brachial blood-pressure of 185/130 mm. Hg. and well marked renal failure. She died shortly afterwards with progressive congestive heart failure. Plate 44, Fig. 12, shows another negative result obtained in a similar case, a girl aged 12, whose brachial blood-pressure was 230/155 mm. Hg. This child had an insidious chronic nephritis and was severely ill at the time her cerebrospinal fluid was tested. She died shortly afterwards with extreme nitrogen retention and generalized anasarca.

In none of the ten patients whose cerebrospinal fluids were tested for melanophore-expanding or oxytocic activity did these tests provide any evidence of the presence of pituitary secretion.

Discussion

The present communication is characterized by a large number of negative results. Since Herring (16) first suggested that posterior lobe secretion passes directly into the cerebrospinal fluid, ample evidence has been accumulated that this occurs in animals. In normal dogs the active principles may be recognized in fresh unconcentrated fluid taken by cistern puncture. It is agreed that the secretion is apparently rapidly absorbed, because fluid withdrawn by lumbar puncture usually contains none of the active principles. In the present investigations sufficient cerebrospinal fluid was taken from each patient to ensure that the latter part came from around the brain-stem so that it was equivalent to fluid taken by cistern puncture. The negative results found in control cases, even with this manœuvre, suggest that the active pituitary principles may be absorbed even more rapidly in man than in the dog. Alternatively it may be that the secretion does not pass so readily from the gland into the cerebrospinal fluid but is distributed rather by the blood-stream.

In patients with high blood-pressure, posterior lobe secretion was found only occasionally in the cerebrospinal fluid. That it was recognized at all shows that in comparison with controls an unusual amount of secretion was present in these few patients. But this is not necessarily evidence of increased secretion by the gland, for there are other explanations such as a decreased rate of absorption of the active principles from the fluid. Never-

theless, if the posterior lobe were to secrete excessively so as to account for pathological actions in the body, it is likely that this secretion would be recognized because the amount then present in the cerebrospinal fluid would be much greater. In the few patients in whom the secretion was detected not more than about 1/500th of a pressor unit per c.c. was found, so that even if the total quantity of cerebrospinal fluid was as much as 200 c.c. it would contain only about one half of a unit in all. Even such small quantities of pituitary secretion could not be detected in most of the patients, so that it is very improbable that 'hyperpostpituitarism' accounts for high blood-pressure either in essential hypertension (hyperpiesia) or in hypertension associated with chronic renal insufficiency whether of primary or secondary origin.

Summary

It is not possible to detect pituitrin in normal unconcentrated human cerebrospinal fluid obtained by lumbar puncture, even if sufficient be taken to make it probable that it comes from the cerebral cisterns.

Patients with essential hypertension or with hypertension associated with chronic renal insufficiency do not usually show an excess of pituitrin in such cerebrospinal fluid. Pituitrin may be detected occasionally, but even then only minute traces are found. The absence of a significant increase is held to be strong evidence that hyperpostpituitarism is not concerned as an aetiological factor in these varieties of hypertension.

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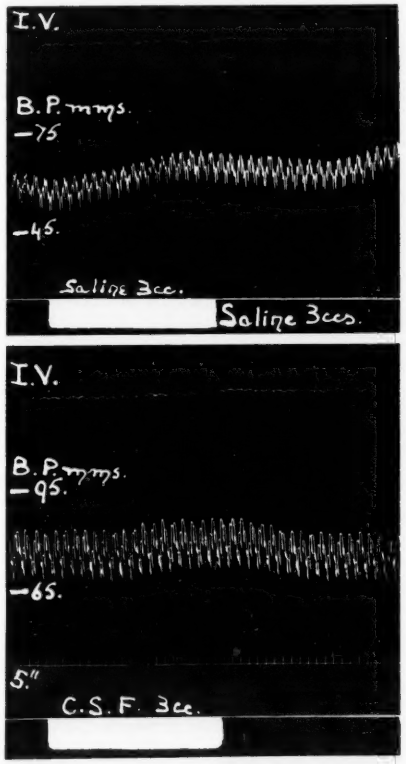

FIG. 1. Cat. Pithed. Artificial respiration. Carotid blood-pressure and intestinal vascular volume. Showing only comparable 'volume effects' from intravenous injection of 3 c.c. saline and 3 c.c. cerebrospinal fluid from hyperpietic patient

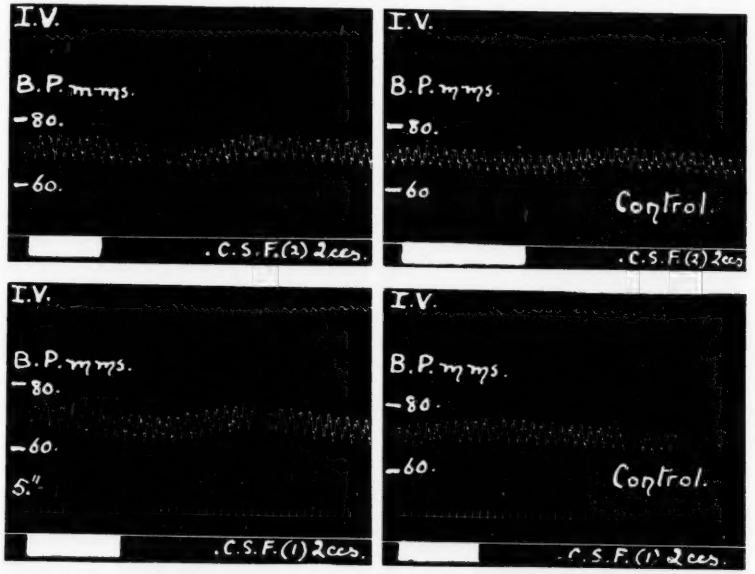

FIG. 2. Cat. Pithed. Artificial respiration. Carotid blood-pressure and intestinal vascular volume. Showing comparative negative results from intravenous injection of two successive samples of cerebrospinal fluid from each of two patients, one with essential hypertension, the other with a chronic duodenal ulcer. (Control)

FIG. 3. Showing comparative effects of intraperitoneal injection in frogs of 3 c.c. cerebrospinal fluid (Frog 1, left), from a patient with essential hypertension, and of 1/40th (Frog 2, centre), and 1/20th (Frog 3, right) unit of 'Pitressin'

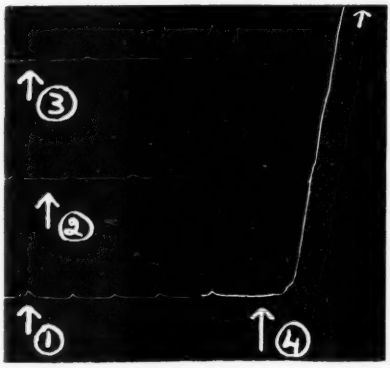

FIG. 4. Showing comparative effects on uterine movements of, (1) 2 c.c. C.S.F. from a control patient, (2) 3 c.c. C.S.F. from a patient with hypertension, (3) 5 c.c. C.S.F. from another patient with hypertension, and (4) 1/20th unit of 'Pitocin'

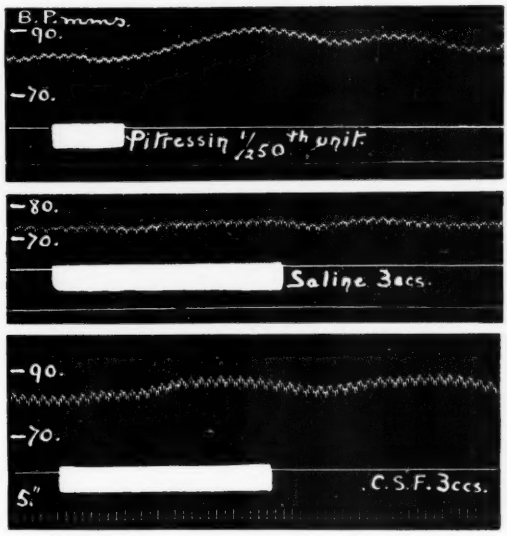

FIG. 5. Cat. Pithed. Artificial respiration. Carotid blood-pressure. Showing effects of intravenous injection of 'Pitressin' 1/250 unit, 3 c.c. saline, and 3 c.c. cerebrospinal fluid from a patient with essential hypertension

hyperpietic patient in this instance had severe paroxysmal dyspnoea when the cerebrospinal fluid was taken. Plate 44, Fig. 10, shows a similar negative result obtained with a patient aged 44, who had a long-standing chronic azotaemic nephritis following upon acute nephritis in adolescence. Although she had few symptoms at the time of these investigations, she had marked cardiovascular hypertrophy with a brachial blood-pressure of 170/105 mm. Hg. and a blood urea of 88 mg. per cent.

Two or more samples of cerebrospinal fluid were usually taken successively and tested separately, but a pressor substance was never detected in a later sample. Plate 44, Fig. 11, illustrates this in the case of a patient, aged 26, who had a chronic nephritis (nephritis repens) with a brachial blood-pressure of 185/130 mm. Hg. and well marked renal failure. She died shortly afterwards with progressive congestive heart failure. Plate 44, Fig. 12, shows another negative result obtained in a similar case, a girl aged 12, whose brachial blood-pressure was 230/155 mm. Hg. This child had an insidious chronic nephritis and was severely ill at the time her cerebrospinal fluid was tested. She died shortly afterwards with extreme nitrogen retention and generalized anasarca.

In none of the ten patients whose cerebrospinal fluids were tested for melanophore-expanding or oxytocic activity did these tests provide any evidence of the presence of pituitary secretion.

Discussion

The present communication is characterized by a large number of negative results. Since Herring (16) first suggested that posterior lobe secretion passes directly into the cerebrospinal fluid, ample evidence has been accumulated that this occurs in animals. In normal dogs the active principles may be recognized in fresh unconcentrated fluid taken by cistern puncture. It is agreed that the secretion is apparently rapidly absorbed, because fluid withdrawn by lumbar puncture usually contains none of the active principles. In the present investigations sufficient cerebrospinal fluid was taken from each patient to ensure that the latter part came from around the brain-stem so that it was equivalent to fluid taken by cistern puncture. The negative results found in control cases, even with this manœuvre, suggest that the active pituitary principles may be absorbed even more rapidly in man than in the dog. Alternatively it may be that the secretion does not pass so readily from the gland into the cerebrospinal fluid but is distributed rather by the blood-stream.

In patients with high blood-pressure, posterior lobe secretion was found only occasionally in the cerebrospinal fluid. That it was recognized at all shows that in comparison with controls an unusual amount of secretion was present in these few patients. But this is not necessarily evidence of increased secretion by the gland, for there are other explanations such as a decreased rate of absorption of the active principles from the fluid. Never-

theless, if the posterior lobe were to secrete excessively so as to account for pathological actions in the body, it is likely that this secretion would be recognized because the amount then present in the cerebrospinal fluid would be much greater. In the few patients in whom the secretion was detected not more than about 1/500th of a pressor unit per c.c. was found, so that even if the total quantity of cerebrospinal fluid was as much as 200 c.c. it would contain only about one half of a unit in all. Even such small quantities of pituitary secretion could not be detected in most of the patients, so that it is very improbable that 'hyperpostpituitarism' accounts for high blood-pressure either in essential hypertension (hyperpiesia) or in hypertension associated with chronic renal insufficiency whether of primary or secondary origin.

Summary

It is not possible to detect pituitrin in normal unconcentrated human cerebrospinal fluid obtained by lumbar puncture, even if sufficient be taken to make it probable that it comes from the cerebral cisterns.

Patients with essential hypertension or with hypertension associated with chronic renal insufficiency do not usually show an excess of pituitrin in such cerebrospinal fluid. Pituitrin may be detected occasionally, but even then only minute traces are found. The absence of a significant increase is held to be strong evidence that hyperpostpituitarism is not concerned as an aetiological factor in these varieties of hypertension.

I wish to thank Dr. Cecil Wall for his valuable advice and criticism. My best thanks are also due to other members of the Honorary Staff who generously allowed me access to their patients. To the original guidance and enthusiasm of the late W. E. Dixon I must acknowledge my deepest indebtedness.

The investigations were made while acting as Medical First Assistant to the Hospital and as Gillson Scholar to the Society of Apothecaries.

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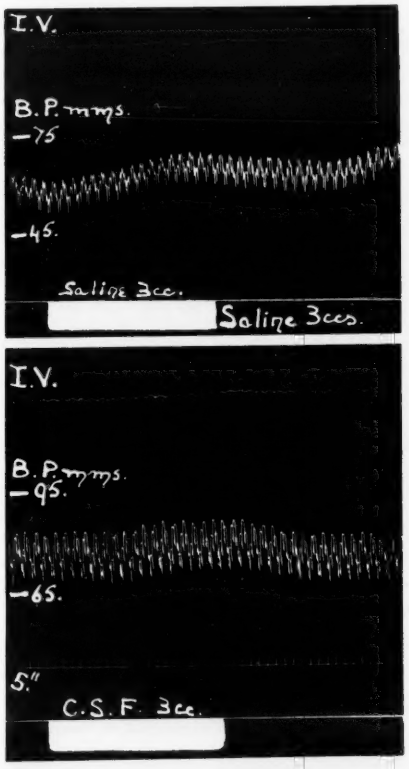


FIG. 1. Cat. Pithed. Artificial respiration. Carotid blood-pressure and intestinal vascular volume. Showing only comparable 'volume effects' from intravenous injection of 3 c.c. saline and 3 c.c. cerebrospinal fluid from hyperpietic patient

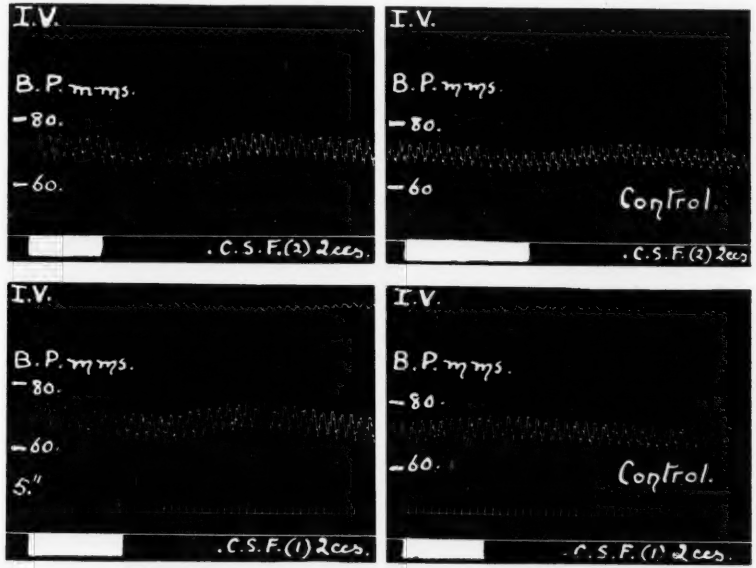


FIG. 2. Cat. Pithed. Artificial respiration. Carotid blood-pressure and intestinal vascular volume. Showing comparative negative results from intravenous injection of two successive samples of cerebrospinal fluid from each of two patients, one with essential hypertension, the other with a chronic duodenal ulcer. (Control)

FIG. 3. Showing comparative effects of intraperitoneal injection in frogs of 3 c.c. cerebrospinal fluid (Frog 1, left), from a patient with essential hypertension, and of 1/40th (Frog 2, centre), and 1/20th (Frog 3, right) unit of 'Pitressin'

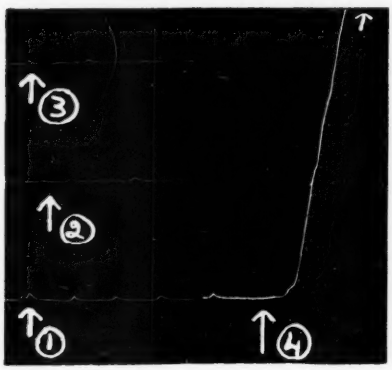


FIG. 4. Showing comparative effects on uterine movements of, (1) 2 c.c. C.S.F. from a control patient, (2) 3 c.c. C.S.F. from a patient with hypertension, (3) 5 c.c. C.S.F. from another patient with hypertension, and (4) 1/20th unit of 'Pitocin'

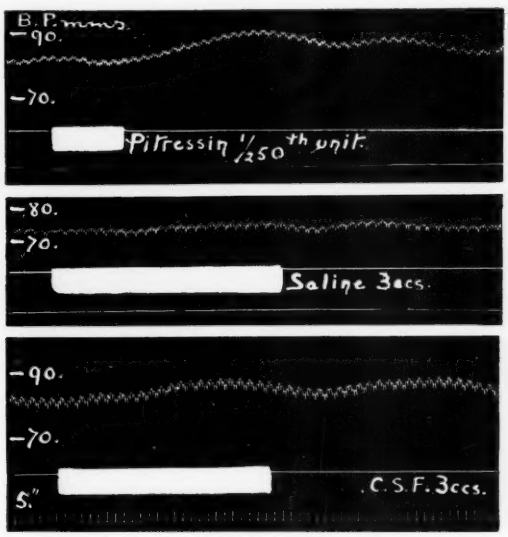


FIG. 5. Cat. Pithed. Artificial respiration. Carotid blood-pressure. Showing effects of intravenous injection of 'Pitressin' 1/250 unit, 3 c.c. saline, and 3 c.c. cerebrospinal fluid from a patient with essential hypertension

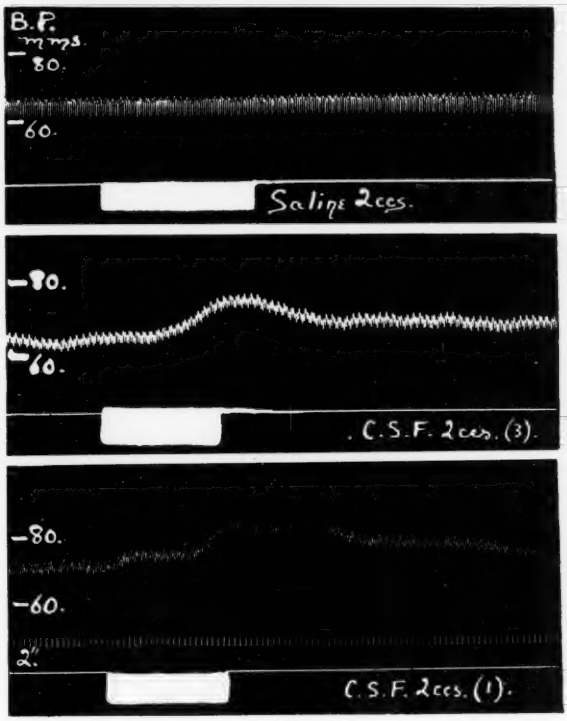


FIG. 6. Cat. Pithed. Artificial respiration. Carotid blood-pressure. Showing effects of intravenous injection of 2 c.c. saline, and 2 c.c. of each of two successive samples of cerebrospinal fluid from a patient with essential hypertension

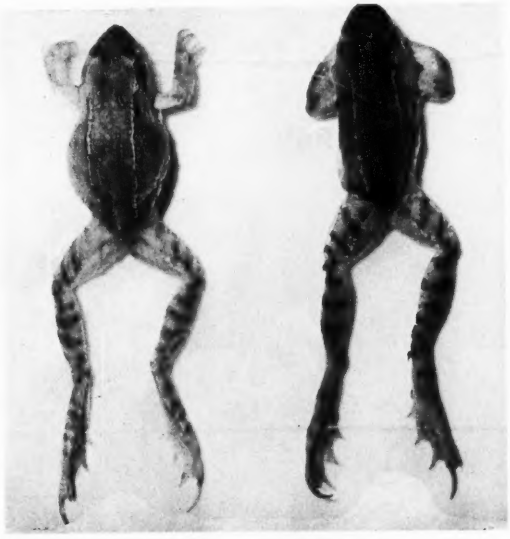


FIG. 7. Showing melanophore-expanding action of cerebrospinal fluid from a patient with essential hypertension. Frog 1 (left), injected intraperitoneally with 0·5 c.c. Ringer's solution as a control; frog 2 (right) injected with 0·5 c.c. cerebrospinal fluid from patient

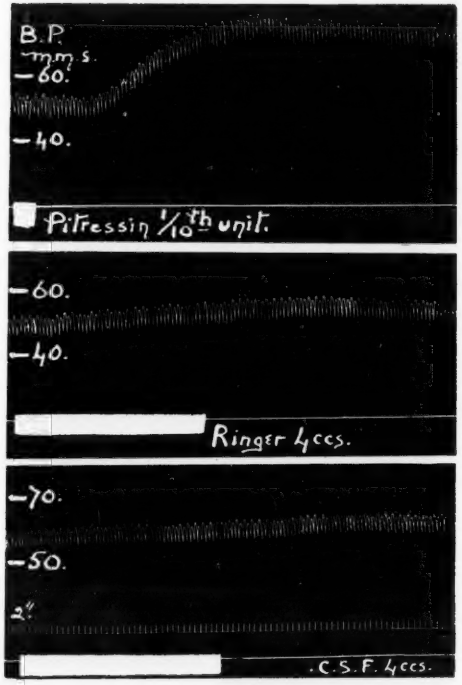


FIG. 8. Cat. Pithed. Artificial respiration. Carotid blood-pressure. Showing comparative effects of intravenous injection of 'Pitressin' 1/10 unit, 4 c.c. Ringer's solution, and 4 c.c. cerebrospinal fluid from a patient with essential hypertension and congestive heart failure

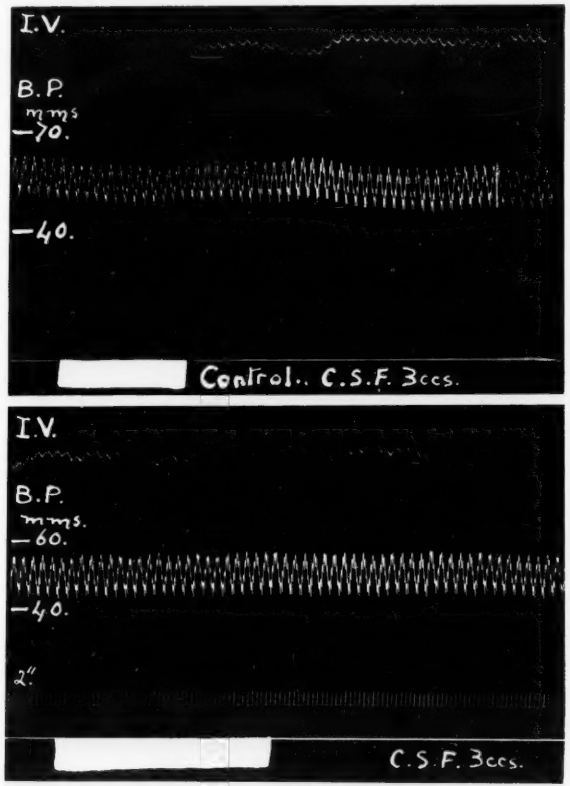
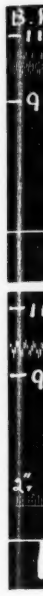


FIG. 9. Cat. Pithed. Artificial respiration. Carotid blood-pressure and intestinal vascular volume. Showing comparable negative results from intravenous injections of 3 c.c. cerebrospinal fluid from a control patient and from a patient with high blood-pressure and chronic renal failure



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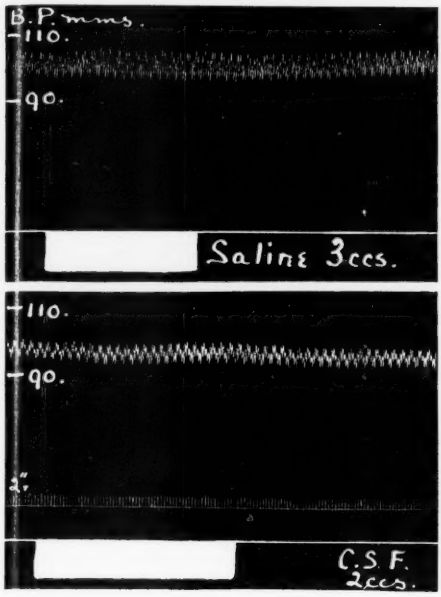

FIG. 10. Cat. Urethane. Vagi cut. Artificial respiration. Carotid blood-pressure. Intravenous injection of 3 c.c. saline as control, and of 2 c.c. cerebrospinal fluid (second 10 c.c. taken) from a patient with hypertension and chronic azotaemic nephritis

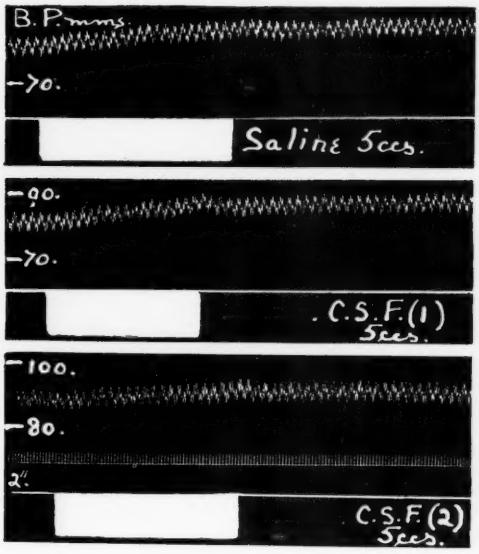

FIG. 11. Cat. Urethane. Vagi cut. Artificial respiration. Carotid blood-pressure. Intravenous injection 5 c.c. saline, and 5 c.c. of each of two successive samples of cerebrospinal fluid from a patient with chronic azotaemic nephritis and high blood-pressure

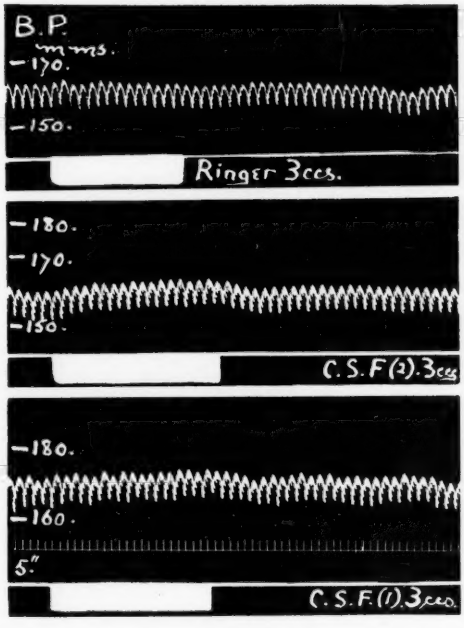

FIG. 12. Cat. Urethane. Vagi cut. Artificial respiration. Carotid blood-pressure. Intravenous injection 3 c.c. Ringer's solution and 3 c.c. of each of two successive samples of cerebrospinal fluid from a patient, aged 12, with chronic nephritis and high blood-pressure

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THE DIAGNOSIS OF ANAEMIA WITH SPECIAL REFERENCE TO CELL VOLUME AND BLOOD-IRON ESTIMATION[1]

By HAROLD W. FULLERTON, ALEXANDER LYALL, and L. S. P. DAVIDSON

(From the Department of Medicine, University of Aberdeen)

Recent studies in haematology have suggested that estimations of the volume and of the iron content of the red cell provide some help in the differential diagnosis of the anaemias. Haden and others in their publications have furnished ample proof that gross departures from the normal in red-cell volume are present in pathological conditions. The literature bearing on the iron content of the red cell is less conclusive, but suggests that much information of value can be derived from this method of examination. Recently, simple methods of estimating cell diameter by diffraction methods have been introduced. Opinion as to the value of these methods is as yet divided. The colour index as a diagnostic criterion is also open to criticism on account of the real difficulty which observers find in estimating slight changes of colour, particularly in the low and high readings, on account of errors of standardization of instruments by manufacturers and of the variation in standards of haemoglobin regarded as normal by different workers in different countries.

The value of the Price-Jones curve as an index of red-cell size is undoubted, but the laborious nature of the procedure and the technical skill required, render this method unsuitable for routine use. The icteric index and Van den Bergh reaction are subsidiary tests in differential diagnosis of haemolytic and non-haemolytic anaemia. Provided hepatitis is excluded, additional information of great value can be obtained from a series of observations after treatment has commenced. In pernicious anaemia the bilirubinaemia is rapidly reduced, whereas in the haemolytic anaemias, such as acholuric jaundice, it is uninfluenced by medical therapy.

It seemed to us that a full investigation of as large a series of different types of anaemia as possible by all the available methods, would form some basis for comparing the value of these different methods in diagnosis.

Before methods requiring special apparatus and technique can be substituted for the simple determination of colour index by red-cell count and haemoglobin estimation, evidence must be produced to show that such

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methods compensate for their increased technical difficulties by providing additional data and increased accuracy in diagnosis.

General Technique of Investigation

The estimations carried out consisted of the following: Haemoglobin estimation (Haldane): red-cell count; white-cell count; differential count; Price-Jones curve; mean cell diameter by diffraction methods; red-cell ratio: total iron estimation; bile pigment estimation by Murphy's method and Van den Bergh reaction. Blood counts in all cases were done on blood collected directly by capillary puncture. For blood-iron, red-cell ratio, and pigment estimation, blood was collected by vein tap in 15 c.c. graduated conical centrifuge tubes, to which two drops of 20 per cent. pure iron-free potassium oxalate had been added and dried. The blood was well mixed and the sample measured immediately for iron estimation. Care was taken that red cells and plasma were well mixed and without bubbles. The blood was then centrifuged for thirty minutes at 2,500 revolutions per minute. We found that no further settling occurred after this period. The total volume of blood and the volume of red cells were then read off and the plasma used afterwards for bile pigment estimation.

Method of Blood-iron Estimation

Numerous methods have been evolved for the estimation of the iron content of the blood. Of the recent colorimetric methods those of Fowweather (1), and of Kennedy (2), have been most widely used. In the present investigations Kennedy's technique, with modifications, has been followed. Difficulty was found in making a standard solution of iron for comparative purposes. The standard solution containing 50 mg. Fe. per cent., used in this work, was made from ferrous ammonium sulphate (Analytic reagent, B.D.H. Ltd.) A weighed quantity, 3·514 grm., of the pure salt, $FeSO_4$ $(NH_4)_2$ SO_4 $6H_2O$, was dissolved in a minimum quantity of distilled water. To this 100 c.c. 10 per cent. sulphuric acid was added and mixed. Then 17 c.c. of pure concentrated nitric acid was added to convert the iron salt to the ferric state. The mixture was allowed to stand over night and made up to 1000 c.c. with distilled water. This solution keeps indefinitely without the formation of any precipitate. The disadvantage of using potassium permanganate to convert the iron salt to the ferric state is that a brown precipitate usually forms on keeping. The standard solution may also be made from analytical iron filings, but the risk of the iron filings containing a proportion of iron hydroxide cannot be easily eliminated. It is important that the standard iron solution should contain its full titre of iron. This could only be ascertained with certainty by titrating the solution for iron element, a process which offers considerable difficulty when the iron has been converted to the ferric state. If the standard iron solution contains less than 50 mg. per cent., the apparent iron values of the blood samples estimated are higher than the true values in proportion to the error present, and consequently the apparent iron indices calculated upon these figures are

higher than the true iron indices. The iron content of a sample standard iron solution used in the present work was checked against a standard solution made under the direction of Professor Alexander Findlay of the Chemistry Department, Aberdeen University. In actual practice we found that the standard solution containing 50 mg. iron per cent. could be used for blood containing over 35 mg. iron per cent. and with haemoglobin above 70 per cent. For blood with iron values below this, i.e., with haemoglobin below 70 per cent., half the quantity of the standard solution was taken for colorimetric estimation, except when very low values were met, when standards containing 15 to 20 mg. iron per cent. were used.

Method. Preliminary experience with the method as described by Kennedy (2) suggested several modifications which we found of advantage. Kennedy recommends digestion over a micro bunsen from the start. We found it more convenient, where a number of estimations were being performed simultaneously, to carry out the first part of the digestion over a sand bath and bunsens in a small Kjeldahl stand. Where the specimen of blood was anaemic, it was usually found that digestion of organic matter was complete within the period of two and a half minutes, as stated by Kennedy, but when blood of normal haemoglobin content was examined it was evident that a further source of oxygen was essential. For this purpose we used additions of 0·5 c.c. perhydrol (Merck), completing digestion over a micro bunsen in the fume cupboard. It was also found advisable to centrifuge the mixture of amylalcoholic extract of iron thiocyanate and water, to clear the amyl alcohol perfectly and rapidly. There was no appreciable loss of amyl-alcohol by evaporation during two minutes in the centrifuge.

Into a 100 c.c. Kjeldahl flask were placed 1 c.c. of well-mixed oxalated blood, 5 c.c. concentrated pure sulphuric acid, and 2 c.c. perchloric acid (sp. gr. 1·12). The mixture was heated over a sand bath until it commenced to clear (in about two and a half minutes). After allowing to cool, 0·5 c.c. perhydrol was added and heat again applied. The flask was then placed sloping over a micro bunsen and one or two further additions of perhydrol used, until the mixture was crystal clear when cold. When cold, one drop of concentrated pure nitric acid was added and 30 c.c. of distilled water ten minutes later. After cooling the mixture was washed quantitatively into a 100 c.c. flask and made up to volume with distilled water. Into a stoppered measuring cylinder were placed 10 c.c. of the diluted blood digest, 10 c.c. of amylalcohol and 5 c.c. of 20 per cent. potassium thiocyanate solution. The fluids were gently mixed and then centrifuged for two minutes to get clear layers. Standard solutions of iron were treated in exactly the same way, taking 1·0 c.c. or 0·5 c.c. of the standard solution containing 50 mg. iron per cent. The coloured solutions of amylalcohol were compared in a Kober-Klett colorimeter.

Definition of Terms

1. The red-cell ratio is the percentage volume of red cells to total blood. We have used the term 'red-cell ratio' in place of the more usual term 'plasma ratio'. The definition shows that the ratio of the red-cell mass to total blood is indicated.

2. The cell-volume index is calculated as

$$\frac{\text{Red-cell ratio, per cent. of normal.}}{\text{Red-cell count, per cent. of normal.}}$$

3. The iron index in the same way is calculated as

$$\frac{\text{Total iron content, per cent. of normal.}}{\text{Red-cell count, per cent. of normal.}}$$

Thus the cell-volume index and the iron index are analogous to the colour index, the normal value being unity and the limits of normal variation for all indices being 0·9 to 1·1. If we accept 46 as the normal red-cell ratio, and 48 as the normal total iron content of the blood, the calculation can be easily illustrated by a typical example. We have, for instance, in a case of pernicious anaemia the following data: Haemoglobin 52 per cent.; red blood-cells 2,200,000; red-cell volume 2·3 c.c.; total volume of blood 9·2 c.c.; total iron content 26 mg. per cent. From such data the following calculations can be made:

(1) Colour index $= \frac{52}{44} = 1{\cdot}2.$

(2) Red-cell ratio $= \frac{23}{92} \times 100 = 25.$

(3) Cell-volume index $= \frac{\frac{25}{46} \times 100}{44} = \frac{54}{44} = 1{\cdot}22.$

(4) Iron index $= \frac{\frac{26}{48} \times 100}{44} = \frac{54}{44} = 1{\cdot}22.$

The haemoglobin saturation index of the red cell can also be calculated, as well as the iron saturation index of the red cell (Reich and Tiedemann) (3).

We have decided to express the iron index in a manner analogous to the colour index and cell-volume index. Murphy, Lynch, and Howard (4), expressed the iron index as the direct quotient of total iron per 100 c.c. of blood and the red-cell count in millions. With this method the iron index varies from five to twenty. The iron-volume index as indicated by Reich is the quotient of the iron content of the blood in percentage of normal, and the cell volume in percentage of normal, and corresponds to what we have called the ' iron saturation index '.

Results in Normal Individuals

A full investigation was carried out in sixteen young, healthy, male adults. Table I shows the results. The average haemoglobin value and red-cell count conform to the accepted standards. The average red-cell ratio agrees with that of Haden (5), but is higher than that found by Murphy and Fitzhugh (6). The average iron content of the blood is 48·8 mg. per cent., with 45 to 54·1 mg. per cent. as the widest variations. The average colour index is 0·99, the average iron index 1·00, and the average cell-volume index 0·99. These figures compare favourably with those found by Murphy, Lynch, and Howard (4). The average value found for the whole blood-iron content in eighteen

healthy adult males by these workers, using the same method, was 44·8 mg. per cent., with 50·0 and 42·0 mg. per cent. as the widest variations. In twenty-one normal young women the average value found was 42·5 mg. per cent., with 46·8 and 38·8 mg. per cent. as the upper and lower limits. The normal red-cell ratio found by these workers was 44·5 for males and 41·2 for

TABLE I

Normals

	Hb.	R.B.C.	R.C.R.	Fe %.	C.I.	C.V.I.	Fe.I.
	100	5·06	43·2	48·1	0·99	0·93	0·99
	106	5·34	43·2	49·5	1·0	0·88	0·96
	97	4·89	40·8	49·0	1·0	0·93	1·05
	110	5·75	46·7	52·0	0·95	0·90	0·94
	109	5·87	46·5	47·8	0·93	0·87	0·88
	95	4·93	40·7	46·5	0·96	1·04	0·98
	100	5·59	47·0	49·6	0·90	0·91	0·93
	100	4·71	47·0	49·5	1·06	1·09	1·09
	95	4·99	50·0	45·0	0·94	1·10	0·95
	93	4·63	41·9	46·5	1·01	0·98	1·04
	95	4·58	41·5	47·1	1·04	1·00	1·06
	110	5·17	50·8	54·0	1·07	1·07	1·08
	100	5·25	47·2	50·0	0·95	0·98	0·99
	108	5·42	49·5	51·8	1·05	1·02	0·99
	96	4·66	46·0	46·2	1·0	1·08	1·03
	107	5·06	50·2	54·1	1·04	1·09	1·11
Average	101	5·1	46·0	48·8	0·99	0·99	1·00
Minimum	93	4·58	40·7	45·0	0·93	0·87	0·88
Maximum	110	5·87	50·8	54·1	1·07	1·09	1·11

females. Our own figure of 46·0 for males compares favourably with the normal taken by Haden and his co-workers (5). We have therefore used 48 mg. per cent. as the normal total iron content of the blood as a basis for calculating the iron index, and 46 as the normal red-cell ratio for the same purpose.

Results in the Anaemias

During the present work, complete investigations of the above nature were made in 31 cases of pernicious anaemia, 25 cases of idiopathic microcytic anaemia, 12 cases of post-haemorrhagic anaemia, and in a miscellaneous group of 28 cases of other blood diseases, including haemolytic anaemias, splenic anaemias, lead poisoning, polycythaemia vera and toxic secondary anaemias.

It very soon became evident that wide differences in the indices under discussion existed in the different groups of anaemias. In pernicious anaemia in particular, the cell-volume index and iron index were found to be high, while in hypochromic anaemias they were low. In post-haemorrhagic anaemias divergence from normal was less marked. Table II is illustrative of typical figures in these groups, where it will be observed that the cell-volume index and iron index are much above unity in pernicious anaemia, and much below unity in idiopathic microcytic anaemia.

Pernicious Anaemia. Several observations were made on each case, making a total of 129 separate investigations in thirty-one cases at all stages in the progress of treatment. Thus in a group of cases detailed information with

TABLE II

	Hb.	R.B.C.	R.C.R.	Blood Fe.	C.I.	C.V.I.	Fe. I.	Icteric index.
Normal	100	5·00	46	48	1·0	1·0	1·0	3
Pernicious anaemia	24	1·02	15	17·0	1·20	1·63	1·78	20
Post-haemorrhagic anaemia	39	3·49	28·5	25·7	0·56	0·89	0·77	2·5
Idiopathic microcytic anaemia	22	3·65	20·0	17·4	0·45	0·58	0·50	2·5

regard to alteration in the various indices in response to treatment became available. The description of a case in full can be taken as illustrating this part of the work.

J. B. Female aged 74. *Pernicious Anaemia.* Was admitted to the Royal Infirmary, Aberdeen, on October 30th, 1931, complaining of extreme weakness.

Previous history and family history—nothing of importance.

Present illness. About May, 1931, the patient became aware of weakness, particularly on exertion. She found it increasingly difficult to carry on her household duties. Breathlessness, palpitation, and dizziness became troublesome features. She noticed that her face was becoming pale and her ankles became swollen at night. There was some loss of weight. During the fortnight before admission anorexia, nausea, and vomiting occurred. 'Pins and needles' in the hands and feet had been present for five weeks.

Examination. Patient was a thin woman and displayed profound pallor and moderate icterus. The tongue was pale and atrophic. There was well-marked arteriosclerosis. A widespread systolic murmur was noted over the cardiac area. Apart from crepitations at the bases of both lungs, examination of the chest was negative. There was no enlargement of the liver and spleen. Examination of the nervous system revealed absence of the deep reflexes. The plantar reflexes were doubtful. No definite area of impaired sensation was present. Ophthalmoscopic examination revealed pale disks and well-marked retinal haemorrhages. The urine showed a trace of albumen and much urobilinogen. There was complete histamine-fast achlorhydria. Blood examination: On admission the blood count was: Haemoglobin 18 per cent.; red blood-cells 940,000; colour index 0·96; white blood-cells 2,500; reticulocytes less than 1 per cent. A blood film showed megalocytosis, extreme anisocytosis and poikilocytosis and occasional megaloblasts. A diagnosis of pernicious anaemia was made, and treatment commenced with daily intramuscular injections of Campolon, followed, after a week, by the administration of a potent fish-liver extract made in Aberdeen. A reticulocyte crisis reaching 20 per cent. began on the fourth day of treatment and improvement was thereafter rapid.

The observations made during recovery are shown in Table III, and three Price-Jones curves made on the 28th, 42nd, and 86th day of treatment are presented in Chart I. The high value of the iron index when the haemoglobin was 18 per cent. is in contrast to the normal figures found for the

colour index and cell-volume index, which, owing to technical difficulties at such a degree of anaemia, are palpably too low.

TABLE III

Case of Pernicious Anaemia During Treatment

Days.	Hb. %.	R.B.C.	R.C.R.	Blood Fe.	C.I.	C.V.I.	Fe. I.	Icteric index.
1	18	0·94	9	18·2	0·96	1·0	2·08	40·0
9	27	1·15	16	17·6	1·28	1·50	1·59	10·0
14	32	1·50	17·4	23·1	1·07	1·25	1·60	7·0
21	40	1·62	17·8	28·0	1·25	1·19	1·82	—
28	50	1·90	21	28·0	1·32	1·20	1·54	2·5
35	55	2·44	21·7	30·8	1·12	0·96	1·31	2·0
42	60	2·53	26	33·3	1·18	1·10	1·38	2·0
56	68	3·43	34·5	40·0	1·00	1·08	1·23	3·0
86	88	4·37	43·0	47·7	1·01	1·06	1·14	3·0

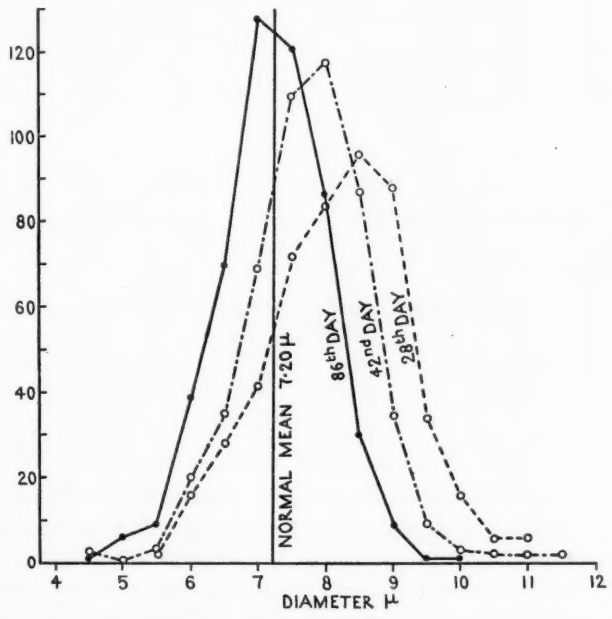

CHART I

J. B. Pernicious Anaemia.

Although the figures from the single case described in detail, show clearly how the indices approach normality under suitable treatment, we considered that an average of the results over the whole series would illustrate this point equally well. Table IV thus represents the results of treatment over the whole series of cases, by grouping single observations according to the haemoglobin level. Only two observations were made in cases with haemoglobin levels below 20 per cent. Here on account of the physical difficulties of measurement, the cell-volume index and colour index were only slightly

increased above normal. The iron index, on the other hand, showed a value of 1·96, accompanied by well-marked haemolytic jaundice. The importance of this observation is discussed later. With haemoglobin values between 20 and 40 the cell-volume index and iron index showed wider deviation from the normal than the colour index. With haemoglobin level between 40 and 60 the same holds true, although in less-marked degree. With higher levels of haemoglobin the iron index still shows a greater degree of abnormality than the others. The cell-volume index and the iron index in particular show a gradual fall as the haemoglobin level rises when thus considered over a series of observations. The high colour index found in the last group is discussed later.

TABLE IV

Pernicious Anaemia

Average Values Grouped for Ranges of Haemoglobin in 129 Observations from 31 Cases

Hb. %.	No. of observations.	Hb.	R.B.C.	R.C.R.	Blood Fe.	C.I.	C.V.I.	Fe. I.	Icteric index.
<20	2	18·5	0·892	8·45	16·1	1·08	1·01	1·96	25
20–40	16	31·3	1·35	16·5	18·8	1·26	1·44	1·59	11
40–60	31	49·6	1·95	23·5	26·9	1·29	1·31	1·43	8
60–80	44	69·2	3·062	31·3	35·0	1·17	1·15	1·24	5
>80	36	87·0	3·805	37·67	43·38	1·20	1·14	1·26	3

TABLE V

Idiopathic Microcytic Anaemia

Average Values Grouped for Ranges of Haemoglobin in 57 Observations from 25 Cases

Hb. %.	No. of observations.	Hb.	R.B.C.	R.C.R.	Blood Fe.	C.I.	C.V.I.	Fe. I.	Icteric index.
<20	2	16·5	3·435	18·7	17·65	0·245	0·60	0·55	7
20–40	15	31·93	3·35	22·83	18·67	0·463	0·75	0·62	4
40–60	17	49·1	4·085	30·6	27·5	0·60	0·815	0·72	4
60–80	15	66·93	4·74	34·4	35·2	0·75	0·82	0·80	3
>80	8	86·5	5·045	40·5	42·3	0·88	0·88	0·88	2

Idiopathic Microcytic Anaemia

Fifty-seven observations were made in twenty-five cases of idiopathic microcytic anaemia (simple achlorhydric anaemia). The average values have been arranged in Table V according to the levels of haemoglobin. A study of this table shows that at low levels of haemoglobin a very low colour index is obtained, which approaches normality at higher levels. The cell-volume and iron indices show much less aberration from normal at low levels of haemoglobin, but agree more closely with the colour index at higher levels. Since haemoglobin deficiency is a much more prominent feature than microcytosis it is suggested that in future this type of anaemia should be named 'Idiopathic Hypochromic Anaemia'. A detailed description of a typical case is given to illustrate these points.

M. L. Female aged 41. *Idiopathic Microcytic Anaemia.* Was admitted to the Royal Infirmary, Aberdeen, on October 1st, 1931, complaining of weakness.

Previous history. During the previous year menstruation had been irregular and the blood loss scanty.

TABLE VI

Case of Idiopathic Microcytic Anaemia

During Treatment

Days.	Hb. %.	R.B.C.	R.C.R.	Blood Fe.	C.I.	C.V.I.	Fe. I.	Icteric index.
1	15	3·70	16·4	16·6	0·2	0·48	0·47	—
34	50	4·56	29·6	30·8	0·55	0·70	0·73	2
41	60	5·20	28·6	32·0	0·6	0·59	0·59	2
54	90	5·57	36·2	36·4	0·81	0·70	0·68	2
73	90	5·55	43·5	49·0	0·81	0·86	0·92	2

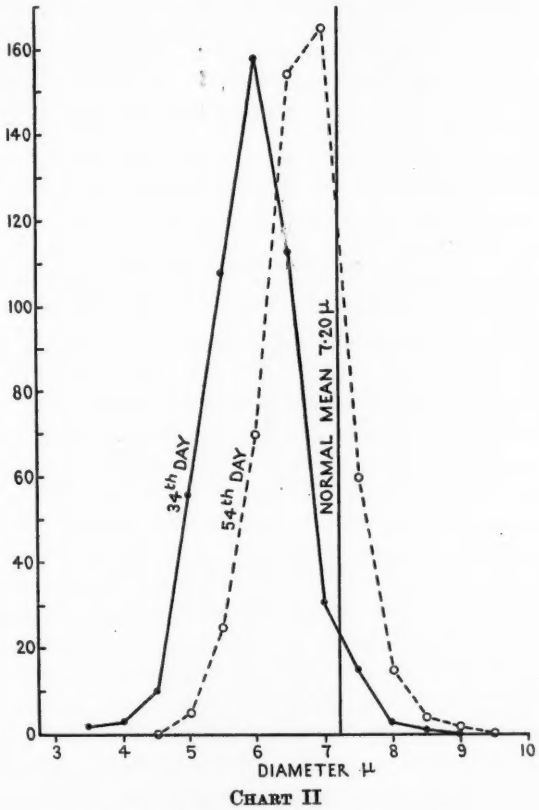

CHART II

M. L. Idiopathic Microcytic Anaemia.

Present illness. Until six months prior to admission the patient had felt in her usual health. She then began to feel weak, and on exertion breathlessness, palpitation, and giddiness occurred. The tongue was frequently sore, and feelings of ' pins and needles ' in the arms and legs had been present for about a year.

Examination. The patient was a well-nourished woman showing extreme pallor without icterus. The tongue was atrophic and inflamed at the edges. The finger-nails were flattened and had lost their lustre. No organic disease was found on examination of the cardiovascular, respiratory, and nervous systems. The spleen was enlarged to the costal margin and was definitely palpable. The urine contained no abnormal constituents. A test meal was given on two occasions and showed an excess of mucus with complete achlorhydria which persisted after the injection of $\frac{1}{2}$ mg. of histamine.

Blood Examinations. On admission the blood count was: haemoglobin 15 per cent.; red blood-cells 3,700,000; colour index 0·2; white blood-cells 7,000; reticulocytes 1·5 per cent.

Differential count. Polymorphs 54 per cent; lymphocytes 42 per cent.; eosinophils 0 per cent.; basophils 0 per cent.; monocytes 4 per cent. A blood film showed very well-marked microcytosis and hypochromia of the red cells. A diagnosis of idiopathic microcytic anaemia was accordingly made, and the patient was treated with iron and ammonium citrate (grains 30 thrice daily). The response to treatment was rapid, and the results of five complete blood investigations are shown in Table VI, and two Price-Jones curves, one done near the beginning and the other near the end of treatment, are shown in Chart II.

The gradual approach of the colour index, cell-volume index and iron index towards normality is well shown in the table.

TABLE VII

Post-haemorrhagic Anaemias

Average Values Grouped for Ranges of Haemoglobin in 41 Observations from 21 Cases

Hb. %.	No. of observations.	Hb.	R.B.C.	R.C.R.	Blood Fe.	C.I.	C.V.I.	Fe. I.	Icteric index.
<20	3	15·3	2·127	12·6	14·6	0·403	0·76	0·797	2·5
20–40	12	31·9	2·51	20·4	20·4	0·65	0·90	0·87	2·5
40–60	17	49·6	3·51	28·01	26·5	0·74	0·88	0·802	2·5
60–80	7	67·57	4·106	33·1	36·3	0·84	0·883	0·934	3
>80	2	90	5·05	40·25	46·0	0·89	0·846	0·966	2

Post-haemorrhagic Anaemias

All anaemias due to acute or chronic haemorrhage are here considered. Reference to differences between the two types will be made later. The results obtained in forty-one observations from twenty-one cases have been grouped in Table VII. At low levels of haemoglobin a low colour index is found. Considerable discrepancy exists between the colour index and the cell-volume and iron indices at these levels, a point which is discussed later. This becomes less apparent at higher levels of haemoglobin, due mainly to an increase in the colour index.

Haemoglobin Saturation Index and Iron Saturation Index

As an alternative method of expressing the haemoglobin content and iron content of the red cell, we have used our data to calculate the satura-

tion indices. These represent the saturation of the cell mass with haemoglobin and iron respectively, and are the quotients of the haemoglobin or iron expressed as a percentage of normal and the red cell ratio as a percentage of normal. Table VIII is condensed from Tables IV, V, and VII,

TABLE VIII

Haemoglobin and Iron Saturation Indices

	Pernicious anaemia.		Idiopathic microcytic anaemia.		Post-haemorrhagic anaemia.	
Hb. %.	Haemoglobin saturation index.	Iron saturation index.	Haemoglobin saturation index.	Iron saturation index.	Haemoglobin saturation index.	Iron saturation index.
<20	1·07	1·94	0·41	0·91	0·53	1·05
20–40	0·88	1·10	0·62	0·83	0·72	0·97
40–60	0·98	1·09	0·73	0·88	0·84	0·91
60–80	1·02	1·08	0·91	0·98	0·95	1·07
>80	1·05	1·11	1·0	1·0	1·05	1·14
Average values in 16 normal individuals:			Haemoglobin saturation index. 1·0		Iron saturation index. 1·01	

and shows the saturation indices for the three types of anaemia. The haemoglobin saturation index is within normal limits in pernicious anaemia at all stages and is low in the more severe degrees of idiopathic microcytic and post-haemorrhagic anaemia, reaching normal values at higher levels of haemoglobin. The iron saturation index in pernicious anaemia falls within the higher limits of normal, except in the very severe stages, where the high indices which occur are partly explained by the inclusion of plasma iron as intracellular iron, a matter which is referred to later. In idiopathic microcytic anaemia the iron saturation index is slightly below normal, except at the higher levels of haemoglobin, while in post-haemorrhagic anaemia the iron saturation of the cell mass is normal. Reich and Tiedemann (3) noted in isolated observations that the iron saturation index in secondary anaemias was usually normal but was somewhat low in cases where there was nutritional disorder. These workers also noted a considerable discrepancy between iron saturation and haemoglobin saturation of the cell mass, which could not be explained on the grounds of experimental error.

Miscellaneous Blood Diseases

This group includes four cases of splenic anaemia (1, 2, 3, 4), four cases of haemolytic anaemia (5, 6, 7, 8), two cases of lead poisoning (26, 27), one of polycythaemia vera (10), and a group of other anaemias partly of toxic origin (Table IX). In the whole group the cell-volume indices and iron indices were below unity, with the exception of three cases of haemolytic anaemia (5, 6, 8), one case of pernicious anaemia in the aplastic stage (11), one case of idiopathic steatorrhoea (12), and one atypical case of pernicious anaemia (28). In the latter three cases indices above normal might be

TABLE IX *Estimations in Miscellaneous Diseases*

Case.	Diagnosis.	Days.	Hb.	R.B.C.	R.C.R.	Blood Fe.	C.I.	C.V.I.	Fe. I.	Icteric index.
1	Splenic anaemia	1	33	3·59	24·0	22·1	0·46	0·70	0·67	5·0
		6	39	3·18	24·0	20·6	0·61	0·82	0·68	4·5
		20	60	4·05	32·9	26·0	0·74	0·88	0·67	3·0
2	Splenic anaemia	1	25	3·29	19·6	19·8	0·39	0·66	0·47	5·0
		14	43	3·58	27·5	26·0	0·61	0·84	0·77	2·5
		28	65	3·94	36·0	33·4	0·83	1·02	0·89	2·0
3	Splenic anaemia	1	26	3·44	18·0	17·8	0·38	0·59	0·56	9·0
		14	33	2·87	21·0	18·1	0·56	0·79	0·70	8·0
		29	68	5·75	28·5	27·2	0·60	0·54	0·50	3·0
4	Splenic anaemia	—	39	3·64	23·2	20·1	0·53	0·70	0·58	2·5
5	Haemolytic anaemia	—	15	0·70	11·0	10·8	1·07	1·70	1·60	60
6	Acholuric jaundice	1	12	0·85	8·0	11·4	0·70	1·02	1·40	50
		15	37	1·73	15·5	21·5	1·06	0·96	1·31	25
		22	42	2·30	13·6	—	0·91	0·64	—	30
		29	46	2·24	19·1	25·5	1·03	0·91	1·19	12
		56	75	4·25	32·2	40·0	0·86	0·83	0·98	3
7	Acholuric jaundice	1	50	2·55	22·0	20·6	0·98	0·94	0·87	7·5
		60	45	2·36	12·9	25·0	0·96	0·59	1·10	30
8	Acquired acholuric jaundice	—	55	2·57	25·2	25·0	1·08	1·07	1·01	25
9	Acute myeloblastic leukaemia	—	16	1·105	10·0	13·4	0·73	0·99	1·28	4
10	Polycythaemia vera	1	150	7·56	64·0	76·9	0·99	0·95	1·06	3
		48	140	7·01	61·0	62·4	1·0	0·93	0·93	2·5
11	Pernicious anaemia in aplastic state	—	38	2·30	22·8	25·0	0·80	1·06	1·14	3
12	Idiopathic steatorrhoea	1	56	2·92	27·9	28·2	0·96	1·03	0·98	3
		9	60	3·43	30·0	32·6	0·88	0·96	1·0	2·5
		15	69	3·13	32·3	34·0	1·11	1·11	1·12	2·5
		30	85	3·51	33·0	38·4	1·21	1·02	1·10	2·5
13	Carcinoma of stomach	–	40	3·70	31·8	21·5	0·54	0·92	0·60	2·5
14	Carcinoma of stomach	—	75	3·62	34·0	34·7	1·04	1·0	1·0	2·5
15	Pulmonary tuberculosis	—	80	4·50	38·0	46·9	0·89	0·92	1·06	3
16	Ulcerative colitis	—	47	2·95	22·9	23·0	0·79	0·85	0·81	2·5
17	Carcinoma of caecum	—	46	3·59	26·6	23·5	0·65	0·80	0·69	2·5
18	Carcinoma of stomach two years after development of pernicious anaemia	1	15	1·94	12·0	10·8	0·38	0·67	0·58	2·0
		15	22	2·51	15·7	14·3	0·44	0·67	0·59	2
		29	26	3·18	23·3	22·8	0·40	0·78	0·75	2
19	Ulcerative colitis	—	45	3·58	26·5	23·4	0·64	0·81	0·69	2·5
20	Portal cirrhosis of liver, with haematemesis	1	39	2·30	24	30·3	0·80	1·13	1·35	15
		9	45	2·30	20·4	34·1	0·97	0·95	1·56	—
		102	70	5·15	32	42·8	0·68	0·66	0·92	7
21	Subacute rheumatism	—	70	3·33	25·0	26·4	0·91	0·82	0·82	2·5
22	Acute rheumatism	—	80	4·98	33·0	36·5	0·81	0·73	0·77	2·5
23	Cellulitis; secondary anaemia	—	30	4·20	25·3	17·3	0·36	0·65	0·43	2·5
24	Congenital syphilis	—	35	3·37	21·0	20·0	0·52	0·68	0·62	5·0
25	Plumbism	1	45	2·84	26·5	25·0	0·79	1·02	0·94	2·5
		7	49	3·37	30·5	35·5	0·73	0·98	1·10	3·5
		14	62	3·80	29·5	32·5	0·82	0·85	0·88	—
26	Plumbism	1	45	2·50	—	24·0	0·90	—	0·98	35
		14	57	3·34	28·6	32·0	0·87	0·93	0·99	12
27	Subacute bacterial endocarditis	1	21	1·86	12·8	12·9	0·57	0·74	0·73	2
		14	35	3·55	29·9	25·0	0·49	0·82	0·96	2·5
		28	44	3·25	21·1	20·7	0·68	0·71	0·80	2
		42	34	2·53	18·8	29·5	0·67	0·80	0·77	2
28	Atypical pernicious anaemia	1	70	3·50	30	38·4	1·02	0·91	1·14	—
		48	80	4·09	37·1	48·0	0·98	0·97	1·20	2
		238	47	2·24	25·5	24·9	1·04	1·24	1·16	2
		448	20	0·93	7·6	9·6	1·07	0·90	1·06	10
		458	40	1·61	21·4	19·2	1·25	1·34	1·34	7

expected. In the cases of haemolytic anaemia the indices were high in the severe stages and were accompanied by well-marked grades of haemolytic icterus. We suggest that under these conditions there is sufficient disturbance of iron metabolism from excessive haemolysis and rapid exchange of iron compounds between the storage depots and the haemopoietic tissues to cause increase in the plasma iron content and an apparent increase of the iron index of the red cell. Since the colour index, cell-volume index, and diffraction reading indicate a mean increase in size of the cell, the increased plasma iron content can only be partly responsible for the increased iron index. This observation to some degree invalidates the statement that high iron indices are present only in pernicious anaemia. But the generalization can be made that a high iron index of the red cell usually accompanies severe degrees of haemolytic anaemia, including pernicious anaemia.

Diffraction Methods

Considerable attention has been paid recently to the fact that a blood film, by acting as a diffraction grating to a source of light, casts circular spectra which vary in size in inverse proportion to the mean diameter of the cells. Pijper (7) laid stress on the accuracy of this method in the diagnosis of pernicious anaemia, and several instruments, varying in detail but alike in principle, have been placed on the market. The success of this method depends primarily on the spreading of a blood film so that the red cells touch tangentially without overlapping. Such a procedure is no easy matter, particularly when severe anaemia is present, since slow spreading of the smear leads to a considerable degree of separation of the red cells, and rapid spreading causes overlapping. The effect of overlapping is obvious, in that it causes a false macrocytosis. This objection becomes increasingly important when it is remembered that the various types of halometer are intended to give a simple method of diagnosis which can be used by general practitioners particularly. All haematologists will agree that the technique of spreading ideal blood films is an art to be acquired only after considerable practice, and it should be pointed out that all films used by us were made by persons well accustomed to the process. Shifting the blood film until the clearest spectra are obtained obviously does not completely overcome this difficulty. Microscopic examination of the smear affords the only proof that any individual area is satisfactorily spread. Another disadvantage of the method depends on the fact that anisocytosis and poikilocytosis cause blurring of the spectra and consequently increase the difficulty of accurate reading. Again, since the reading depends in all types of instrument on colour perception, the personal factor becomes of great importance. All the estimations here considered were made by the same person, in order to overcome this difficulty. Two instruments were used, one of which was made for us by Mr. Harry D. Griffith, of the Natural Philosophy Department, Aberdeen University, to whom our thanks are due. The spectra were

projected on a ground-glass screen and measurements made by calipers. By this method a well-spread film with little anisocytosis or poikilocytosis gives rise to two, or sometimes three, concentric spectra. Measurements were made of the inner diameters of the red rings of the two innermost spectra. A variation between 7 to 7·5 mm. for the inner ring, and 14 to 15 mm. for the outer ring, was considered within normal limits. This indicated a mean cell diameter of from 7·3 to 7·8 μ. Ewles halometer was the other instrument used. Here the diameter of the red ring of the spectrum is compared with the distance between two fixed points. Readings were considered normal when these points fell within the inner and middle diameters of the red ring. Altogether 147 films were examined from sixteen cases of pernicious anaemia, thirty-five cases of idiopathic microcytic anaemia, and fourteen cases of post-haemorrhagic anaemia of all degrees of severity.

TABLE X

Diffraction Readings

(1) *Special Halometer*

(*a*) Where innermost ring is taken as index of mean cell diameter.

	Number of observations.	Macro-cytosis.	Normo-cytosis.	Micro-cytosis.
Pernicious anaemia	31	19 (61 %)	9 (29 %)	3 (10 %)
Idiopathic microcytic anaemia	92	23 (25 %)	57 (62 %)	12 (13 %)
Post-haemorrhagic anaemia	24	3 (12·5 %)	18 (75 %)	3 (12·5 %)

(*b*) Where outer red ring is taken as index of mean cell diameter.

Pernicious anaemia	31	21 (68 %)	10 (32 %)	0
Idiopathic microcytic anaemia	92	8 (9 %)	75 (82 %)	9 (10 %)
Post-haemorrhagic anaemia	24	1 (4 %)	23 (96 %)	0

(2) *Ewles Halometer*

Pernicious anaemia	23	13 (56·5 %)	10 (43·5 %)	0
Idiopathic microcytic anaemia	74	9 (12 %)	48 (65 %)	17 (23 %)
Post-haemorrhagic anaemia	21	2 (10 %)	15 (71 %)	4 (19 %)

The results are shown in Table X, arranged according to the type of anaemia without regard to the severity. It will be seen that when the special halometer is used, films from cases of pernicious anaemia indicate macrocytosis in over 60 per cent. of cases, but macrocytosis is indicated also in a proportion of the microcytic anaemias. Price-Jones curves and cell-volume index estimations clearly demonstrated that these readings were fallacious. These errors were due to failure in obtaining even spreading of the films, overlapping of the cells, and to the difficulty of making accurate measurements, due to blurring of the haloes consequent on the marked anisocytosis and poikilocytosis which were found in some of the microcytic anaemias with very low counts. In a few cases an increase in the diameter readings may have been due to the presence of a reticulocyte crisis consequent on iron therapy. Reticulocytes, as is well known, have a greater diameter than mature corpuscles. Ewles halometer gave no better results.

In conclusion it may be said that, while such instruments may be useful to haematologists in affording confirmative means of diagnosis under certain conditions, they are unreliable as a single method of diagnosis. The chief objection to diffraction methods is that they suggest to the general practitioner that he has at his disposal a means by which he can make a simple, rapid, and accurate diagnosis of the type of anaemia present without the assistance of a full haematological examination. We are of opinion that such a conclusion is not only unjustified but may be a source of danger to the patient.

Consideration of Results

Cell-volume index. In considering the results of the work presented here it is evident that gross variations from normal occur in the cell-volume index in the anaemias, particularly in idiopathic microcytic anaemia and in pernicious anaemia. Our results are in accordance with the published findings of Haden (5). The smallest cell volume found by this worker in anaemia due to a qualitative defect in blood formation, including achlorhydric anaemia, was 0·63, and the average value for this group of his cases was 0·86, while for pernicious anaemia the figures were 1·13 (minimum), 2·24 (maximum) with an average of 1·43. In our series the cell-volume index varied from 0·58 to 1·13 in idiopathic microcytic anaemia (average 0·80), while in pernicious anaemia the figures lay between 0·84 and 1·79, with an average of 1·22. Additional data obtained from repeated examinations during treatment indicate that the cell-volume index, Price-Jones curves and diffraction readings approach normal when a satisfactory haemopoietic response has been obtained.

Iron index. The iron index of the red cell also varies through wide limits in the anaemias. In idiopathic microcytic anaemia the reduction in iron index is, however, less marked than the increase in this index in pernicious anaemia. The shift to the right or left respectively is analogous to that shown by the Price-Jones curve. In the accompanying Chart III we have plotted the number of estimations in the ordinate and iron index in the abscissa. The peak for all stages of treatment in microcytic anaemia lies over 0·7, and for pernicious anaemia at 1·3. For comparison the colour indices are shown in the same graph. The peak for colour index both for pernicious anaemia and idiopathic microcytic anaemia is farther to the left than in the case of the iron index.

It has been noted from Table IV that there is little tendency in the higher ranges of haemoglobin for the colour index to reach normality. In searching for an explanation of this phenomenon it was discovered that a number of the cases having haemoglobin values greater than 80 per cent. were chronic cases, resistant to treatment and frequently showing subacute combined degeneration of the cord and a persistent macrocytosis. Accordingly those cases having red-cell counts above 4,000,000 were grouped as shown in

Table XI. It will be seen that the average colour index is unity, while the iron index and cell-volume index fall within the upper limits of normality. This is in keeping with the recognized fact that when the stage of remission is well established the blood picture returns to normal.

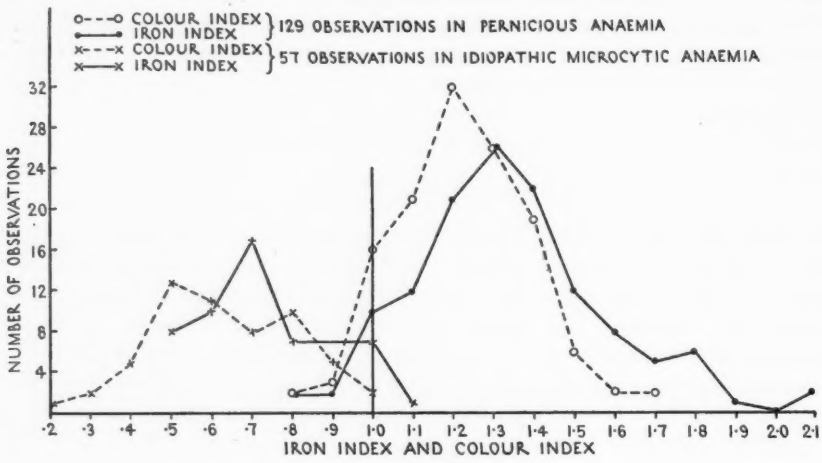

CHART III

TABLE XI

Eleven Observations in Seven Cases of Pernicious Anaemia with Red-cell Counts Greater than Four Million

	Hb. %.	R.B.C.	R.C.R.	Blood Fe.	C.I.	C.V.I.	Fe. I.	Icteric index.
	95	4·22	45·5	54·0	1·13	1·18	1·32	7·0
	70	4·20	38·0	44·0	0·83	0·97	1·09	3·5
	92	4·97	38·4	43·0	0·93	0·84	0·90	2·5
	88	4·37	43·0	47·7	1·01	1·06	1·14	3
	90	4·14	47·3	46·0	1·09	1·24	1·15	2·5
	85	4·34	40·5	43·5	0·98	1·02	1·04	3·0
	86	4·21	40·0	43·0	1·01	1·10	0·98	3·0
	80	4·12	40·1	39·0	0·97	1·07	1·01	2·5
	84	4·25	39·5	43·2	0·98	1·02	1·06	6·0
	95	4·28	48·5	54·8	1·12	1·24	1·33	2·5
	88	4·61	39·5	45·5	0·96	0·93	1·03	3
Average	86·6	4·34	41·85	45·8	1·001	1·06	1·095	3·5

Discussion

As indicated earlier, the main object of these investigations was to collect data for the purpose of comparison and evaluation of the various methods available for diagnosis in the anaemias. We have directed attention particularly to the relative value of the colour index, the cell-volume index, and the iron index. These indices are grouped and compared in Table XII. In

pernicious anaemia 2·3 per cent. of observations show colour index, iron index and cell-volume index below normal. The colour index and cell-volume index fall within normal limits in 20 per cent. of observations, while normal iron index values occur in only 14·7 per cent. of estimations. Values in the normal and subnormal ranges occurred in the stages of remission. (See Table XI). All iron and cell-volume indices were above unity, without exception, in observations in pernicious anaemia with red-cell counts below

TABLE XII

Group 1. Pernicious Anaemias. 129 Estimations

C.I.	Greater than normal in 99 estimations	= 76·8 %
	Normal in 27 estimations	= 20·9 %
	Less than normal in 3 estimations	= 2·3 %
C.V.I.	Greater than normal in 96 estimations	= 74·4 %
	Normal in 30 estimations	= 23·3 %
	Less than normal in 3 estimations	= 2·3 %
Fe. I.	Greater than normal in 107 estimations	= 83 %
	Normal in 19 estimations	= 14·7 %
	Less than normal in 3 estimations	= 2·3 %

Group 2. Idiopathic Microcytic Anaemias. 57 Estimations

C.I.	Less than normal in 54 estimations	= 94·7 %
	Normal in 3 estimations	= 5·3 %
	Greater than normal in 0 estimations	= 0 %
C.V.I.	Less than normal in 42 estimations	= 73·7 %
	Normal in 13 estimations	= 22·8 %
	Greater than normal in 2 estimations	= 3·5 %
Fe. I.	Less than normal in 46 estimations	= 80·7 %
	Normal in 11 estimations	= 19·3 %
	Greater than normal in 0 estimations	= 0 %

Group 3. Post-haemorrhagic Anaemias. 41 Estimations

C.I.	Less than normal in 35 estimations	= 85·4 %
	Normal in 6 estimations	= 14·6 %
	Greater than normal in 0 estimations	= 0 %
C.V.I.	Less than normal in 24 estimations	= 58·6 %
	Normal in 16 estimations	= 39 %
	Greater than normal in 1	= 2·4 %
Fe. I.	Less than normal in 23 estimations	= 56·1 %
	Normal in 16 estimations	= 39 %
	Greater than normal in 2 estimations	= 4·9 %

(Limits of normality for indices 0·9–1·1)

3,500,000. On the whole it can be said that the iron index is a better diagnostic test for megalocytic anaemia than either the cell-volume index or colour index. This is particularly true for the low ranges of haemoglobin, owing to certain technical difficulties already mentioned, but the margin of difference becomes progressively less with higher ranges of haemoglobin, until during remission the indices all approach unity. It is extremely important to decide whether the cell-volume index and iron index afford any real advantage over the colour index at the stage when diagnosis may be

difficult, i.e. with a red-cell count over 4 million and a colour index approaching unity. It would seem to us from a close analysis of the figures presented that the iron index and cell-volume index, while affording valuable confirmatory evidence, show little advantage over the simple determination of the colour index in the diagnosis of pernicious anaemia. Of the two methods the cell-volume index is easily carried out, while the estimation of the blood iron is a highly technical and difficult procedure. Furthermore, it must be remembered that the iron index of the red cell may be above unity in severe anaemias other than pernicious anaemia. This phenomenon is seen in haemolytic anaemias accompanied by hyperbilirubinaemia as demonstrated in the group of miscellaneous anaemias. (See Table IX.) In cases of this type the disappearance or persistence of increased bile-pigment content of the serum assumes importance in diagnosis, as does estimation of cell fragility and spontaneous reticulocytosis.

In considering the hypochromic anaemias (Groups II and III, Table XII), it is clear that the colour index affords more reliable diagnostic information than either the cell-volume index or the iron index. Not only is the percentage of cases with normal values for colour index much less, but the degree of variation from the normal is greater. The iron index shows the greatest incidence of normal values in undoubted hypochromic anaemia and is therefore the least valuable of the three methods for the diagnosis of this group.

The question arises whether these additional tests are of value in separating cases of idiopathic microcytic anaemia from post-haemorrhagic anaemias. A study of Tables V and VII shows that all three indices in the lower ranges of haemoglobin tend to be higher in post-haemorrhagic anaemia than in idiopathic microcytic anaemia. These differences are not sufficiently large to be of definite value in the individual case. Moreover, when the cases of post-haemorrhagic anaemia are divided into those resulting from acute and chronic haemorrhage respectively, it is found that the latter group have indices identical with those present in idiopathic microcytic anaemia. The higher level of all indices in the post-haemorrhagic group is therefore due to the inclusion of cases of anaemia following acute blood loss. In acute haemorrhage where the blood volume is suddenly depleted, it is natural for the remaining cells to show normal characteristics. If the investigation is made during a reticulocyte crisis which has occurred as the result of a massive haemorrhage or from iron therapy, an increase in the cell-volume index may be found. This explains the three cases showing values greater than normal in Groups II and III. Confirmatory evidence was afforded by Price-Jones curves and diffraction readings.

If Haden's (5) figure for normal haemoglobin values (15·4 grm. per cent.) and Murphy's (6) figures for normal red-cell ratio (42·9), and for blood-iron (4) (45·0), are accepted, in place of the lower values for haemoglobin (13·5) and higher values for red-cell ratio (46·0) and for iron (48·0), upon which we have based our calculations, then obviously our results in macro-

cytic anaemia would show a still greater deviation from the normal in cell-volume index and iron index. Therefore these tests would appear to have a definite advantage over the colour index. Since, however, the same factors must apply to microcytic and normocytic blood, the cell-volume index and iron index in these conditions would approach and exceed normality in a higher percentage than is shown in our own figures. This disadvantage more than outweighs the apparent value of the high indices which Haden and Murphy obtained in macrocytic anaemia. Our standards when applied to normal blood clearly showed that the three indices were comparable, since a figure of unity was obtained for all. Moreover, in our studies of hypochromic anaemia we find normal values for cell-volume index and iron index in more than 20 per cent. of estimations, compared with 5 per cent. normal values for the colour index. Accordingly we are not prepared to increase this discrepancy by altering our standards.

During the progress of this work a number of interesting minor observations were made. We were impressed by the lack of correspondence between the colour index and the iron index. In practically all observations in the anaemias the iron index showed higher values than the colour index. This generalization applied to pernicious anaemia and microcytic anaemia alike, and was most marked at low levels of haemoglobin. It might be suggested that this phenomenon can be explained by the fact that too low a standard of normality for blood iron was taken or that the standard solutions of iron used were under their true titre. In actual fact the standard taken for normal iron values here exceeds that accepted by Murphy, Lynch, and Howard, and the iron solutions used were carefully checked. In addition, amongst the observations on normal individuals no such discrepancy occurred. (See Table I.) Previous observers have noted particularly in pernicious anaemia that the actual iron content of the blood was greater than the iron content calculated from the observed haemoglobin value. Fowell (8) noted this discrepancy as early as 1912 and suggested that iron might be present in the red cell in some form other than haemoglobin. In seven observations in pernicious anaemia the iron indices as calculated by our method from the figures given by Fowell varied from 1·5 to 2·8, while the colour indices varied from 1·2 to 1·9. Fowell deserves the credit for the earliest observation of this phenomenon, which has been amply confirmed by recent workers. Reich and Tiedemann (3) noted the same fact and suggested that this excess of iron might be present in a prehaemoglobin state or in the form of some decomposition product of haemoglobin. From our own figures it is evident that the greatest discrepancies exist in the lower values of haemoglobin. This phenomenon is no doubt partly explained by the fact that plasma iron is estimated as well as intracellular iron in the total iron estimation of the blood. The plasma iron normally does not often exceed 1 mg. per cent. Riecker (9) found that the serum iron for forty normal individuals varied between 0·9 and 1·4 mg. per cent. This value would make only a small percentage difference to the

calculated iron index where the total blood-iron value is in the normal ranges (48 mg. per cent.). But where the total iron content has decreased to values below 20 mg. per cent., and where the plasma iron has increased to 2 mg. per cent., the latter fraction forms 10 per cent. of the total iron in the circulation. These changes occur simultaneously in the severe stages of pernicious anaemia and are responsible at least for a part of the increase of the iron index of the red cell. While this hypothesis is satisfactory for the relapsed stage of pernicious anaemia where haemolysis is at its maximum, it cannot be the whole explanation, since this divergence is still present at higher levels of haemoglobin where the icterus index is normal, and also in microcytic hypochromic anaemia. Accordingly, it appears to be necessary to subscribe to the views of Fowell (8), and of Reich and Tiedemann (3) that iron may be present in the red cell in forms other than haemoglobin. We must beware of assuming that a high iron index is diagnostic of pernicious anaemia, since our studies of haemolytic anaemias, acquired or congenital, show similar figures in the severe stages, an observation which shows the dangers of establishing a diagnosis on any single criterion.

Data regarding red-cell counts, red-cell ratios and haemoglobin, and iron estimations presented in this paper were obtained by the independent observations of the authors, all of whom have had a wide experience in this field. Nevertheless a study of the tables reveals some discrepancies between the three indices which can only be the result of technical errors. It is certain that in the hands of less experienced individuals these errors would have been more frequent and of greater magnitude. The chief discrepancy lies in the estimation of haemoglobin, particularly in the low and high readings in which colour discrimination is especially difficult. With a haemoglobin of 15 per cent. or less, it is essential to withdraw two pipettefuls of blood, in order to produce any accuracy in matching the colour standards. This practice itself leads to obvious errors. Moreover, in anaemias of such severity marked tissue oedema may be present, which by diluting the blood obtained by capillary puncture, may produce figures markedly too low. We have verified this fact by comparing haemoglobin readings of blood obtained by capillary puncture and by vein tap. In conclusion it can be stated that for satisfactory haematological diagnosis advantage should be taken of all available data, both clinical and laboratory, and the careful study of a stained blood film should never be omitted, since it affords information regarding qualitative changes in the cells, such as anisocytosis, poikilocytosis, and ovality, which is of great importance.

Summary

For the purpose of comparing the value in diagnosis of the colour index, cell-volume index and iron index, a full haematological investigation was made, comprising 129 observations in pernicious anaemia, 57 in idiopathic

microcytic anaemia, 41 in post-haemorrhagic anaemia, and 57 in other anaemias.

In all types of anaemia, and at all stages, the indices run parallel to one another. The cell-volume index, and particularly the iron index, gave higher readings than the colour index. The advantages claimed for these methods in the diagnosis of macrocytic hyperchromic anaemia are confirmed, but are offset by increased difficulty in the diagnosis of microcytic hypochromic anaemia. Accordingly the colour index, if accurately estimated, still remains a simple and satisfactory procedure for routine diagnostic purposes; but for difficult cases and research work the addition of one or both of the subsidiary methods affords a valuable check. The results of investigations into cell diameter, blood-pigments, and iron metabolism are presented.

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PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

MINUTES OF GENERAL MEETING, 1933

THE TWENTY-SEVENTH ANNUAL GENERAL MEETING was held in Glasgow on Friday and Saturday, April 7 and 8, 1933. The meetings were held in the Zoology Department of the University. The Attendance Book for the Meeting was signed by 167 members. The proceedings began at 10 a.m.

The President, Professor T. Gillman Moorhead, was in the Chair.

The Minutes of the last Annual Meeting having been published in the *Quarterly Journal of Medicine*, were taken as read and confirmed.

Presentation of the Treasurer's Accounts. Dr. Morley Fletcher, Treasurer, presented the Annual Accounts. They showed a balance of £484 14*s.* 3*d.* Dr. Fletcher explained that the apparent increase in the balance was due to the fact that the bill for the *Quarterly Journal of Medicine* had not yet been paid for the year as it had not been received from the Clarendon Press. The expenditure was otherwise normal.

Selection of Place of Meeting for 1934. A letter was read from Dr. Veale on behalf of the local members, inviting the Association to meet at Leeds. The invitation was cordially accepted. An invitation had also been received from Manchester.

Election of Officers

President. Professor T. K. Monro was elected President for 1933–4. On his election he took the Chair, and expressed the thanks of the Association to the retiring President for his services during the past year.

Election of Members of the Executive Committee, Honorary Members, Extra-ordinary Members, and Ordinary Members followed:

Treasurer. Dr. H. Letheby Tidy.

Secretary. Dr. L. J. Witts.

Members for England:

Professor T. Beattie.
Sir J. Charlton Briscoe.
Dr. J. le F. C. Burrow.
Dr. M. A. Cassidy.
Dr. J. G. Emanuel.
Dr. H. Thursfield.

Members for Scotland:

Dr. D. Campbell.
Dr. J. Carslaw.
Dr. J. Eason.

Members for Ireland:

Dr. Rowland Hill.
Dr. J. C. Rankin.
Dr. R. J. Rowlette.

As Extra-ordinary Members:

Dr. E. J. Cave.
Dr. J. R. Charles.
Dr. D. Lawson.
Dr. A. G. Phear.

As Honorary Members:

Professor T. Gillman Moorhead, M.D. (President 1932–3).
Dr. H. Morley Fletcher (Secretary 1920–26; Treasurer 1926–33).

As Ordinary members:

Harold Esmond Arnison Boldero, M.D., Assistant Physician, Middlesex Hospital.

Ernest Bulmer, M.D., Assistant Physician, General Hospital, Birmingham.

Philip Cyril Powter Cloake, M.D., Physician, Queen's Hospital, Birmingham.

Kenneth Edwin Harris, M.D., Assistant Physician, University College Hospital.

David Kennedy Henderson, M.D., Professor of Psychiatry, University of Edinburgh.

Theo Jenner Hoskin, M.D., Physician, Royal Free Hospital.

John Clifford Hoyle, M.D., Medical First Assistant, London Hospital.

George Johnson Langley, M.D., Physician, Ancoats Hospital, Manchester.

Edwin Charles Warner, M.D., Assistant Physician, Charing Cross Hospital.

John Frederick Wilkinson, M.D., Director of Research, Manchester University.

William Gifford Wyllie, M.D., Assistant Physician, Hospital for Sick Children, Great Ormond Street.

Vote of Thanks to the Retiring Honorary Treasurer. The President moved a hearty vote of thanks to the retiring Treasurer, Dr. Morley Fletcher, for his long services to the Association. He had acted as Treasurer for seven years, and previous to that as Secretary for a further seven years. He had been a member of the Executive Committee for nearly twenty years. The Association had already elected him as an Honorary Member. The vote of thanks was passed amid general applause.

Other Business. Sir James Purves-Stewart raised the question whether the title 'Emeritus Members' would not be more honorific than the title 'Extra-ordinary Members'. He gave notice that he would move a motion at the next Annual General Meeting.

The Annual Dinner. The Annual Dinner was held at the Central Hotel. The President, Professor T. K. Monro, was in the Chair. The official guests included the Principal of the University, the Lord Provost, Dr. Barclay Ness, the President of the Royal Faculty of Physicians and Surgeons, and Colonel Mackintosh, Superintendent of the Western Infirmary. 102 Members and guests were present.

SCIENTIFIC BUSINESS

Friday Morning

1. Dr. A. Lyall and Dr. H. W. Fullerton (introduced) discussed *The Comparative Values of Cell-volume Index, Iron Index, and Colour Index in the Diagnosis of Blood Diseases.* The investigation of 25 cases of pernicious anaemia, 18 cases of post-haemorrhagic anaemia, and 31 other cases of other anaemias followed throughout the course of treatment, showed that the cell-volume index varied from 0·53 in idiopathic microcytic anaemia to 1·96 in pernicious anaemia, and that the iron index varied from 0·5 to 2·24 in the same respective diseases. In pernicious anaemia the cell-volume index and iron index were found to furnish valuable collateral information in diagnosis. These indices showed return towards normal values under treatment.

In the discussion which followed Dr. Witts urged that Price-Jones' count of the cell size should be included in such investigations.

Drs. Stanley Davidson, Campbell, and Parkes Weber joined in the discussion.

2. Professor L. S. P. Davidson reported *Investigations into the Relations of Vitamin B to Anaemia.* 14 cases of pernicious anaemia were treated with Marmite or alcoholic extracts made therefrom. Treatment was successful in three cases and failed in 11, although subsequent liver or liver extract therapy was satisfactory. It is concluded, therefore, that Marmite in its present form cannot be used as a substitute for liver or liver extract in the treatment of pernicious anaemia.

Dr. Goodall stated that Marmite was useful in nearly all cases of pernicious anaemia in the initial attacks and also to maintain recovery.

Dr. Ungley (introduced) also spoke.

3. Dr. Donald Hunter described *Conditions simulating Generalised Osteitis Fibrosa.* Differences were pointed out in the history, clinical course, physical signs, blood chemistry, and radiograms, of the following diseases:—

(*a*) Of bone—focal osteitis fibrosa, osteomalacia, osteoclastic carcinomatosis, and osteitis deformans.

(*b*) Of cartilage—enchondromata, dyschondroplasia with ossifying ecchondromata, and unilateral dyschondroplasia (Osler).

(*c*) Of marrow—multiple myelomatosis, xanthomatosis (Schüller-Christian), and Gaucher's disease.

The communication was illustrated by lantern slides of bone radiograms.

4. Dr. N. Morris discussed *Carbohydrate and Nitrogen Absorption in Coeliac Disease.* A flat blood-sugar curve is not pathognomonic of coeliac disease but is found occasionally in marasmus. The addition of fat to glucose also reduces the height of the blood-sugar curve even in health. The blood non-protein nitrogen curve after ingestion of urea shows a delayed fall in coeliac disease. This can be simulated in health by the addition of fat to the urea ingested. The absorption and renal excretion and concentration of urea appear to be quite good in coeliac disease.

Drs. Ryle, Coope, and Izod Bennett discussed this communication.

5. Dr. J. B. Rennie (introduced) discussed *The Serum Protein in Various Types of Oedema.* Serum proteins were below the level associated with oedema in two cases of nutritional oedema (four observations) and in two cases of the nephrotic syndrome (16 observations). In cardiac failure—three cases (three observations)—reduction of serum albumin played a part in the production of oedema. Although in 47 cases of acute nephritis diminution of serum proteins was not solely responsible for oedema, the lower the serum protein, the more marked was the oedema. Serum proteins were below oedema level in nine cases of nephritis in infants under eighteen months.

6. Dr. W. A. R. Thompson (introduced) discussed *The Plasma Proteins and Cardiac Oedema.* A distinct diminution in the protein content and colloid osmotic pressure of the blood had been found in cases of cardiac oedema. Of cases of cardiac oedema, 87·5 per cent. had a plasma albumin content below 3·2 grm. per cent., and 91 per cent. had a colloid osmotic pressure below 29 cm. of water, while of cases of heart disease without oedema, only 13 per cent. had a plasma albumin content below 3·2 grm. per cent., and 9 per cent. had a colloid osmotic pressure below 29 cm. of water. It was suggested that this decrease in the colloid osmotic pressure of the blood, resulting from a diminution of the plasma proteins, might be a factor in the causation of cardiac oedema.

7. Dr. F. Parkes Weber spoke of *An Unusual Variety of Urticaria Pigmentosa in Adults.* This he had termed 'telangiectasia macularis eruptiva perstans' before he recognized that it was probably a telangiectatic and relatively pigmentless variety of urticaria pigmentosa of adults. It was apparently the same condition as Sir W. Osler had described in 1907 under the heading 'telangiectasia circumscripta universalis' and L. Brocq and others in France had called 'telangiectasies acquises généralisées' or 'télangiectasies essentielles en plaques acquises'. The illustrations shown were from the cases described by Weber and Hellenschmied, Barber and Weber, and Sir William Osler.

2 p.m. to 3 p.m.

Demonstration of Clinical Cases at the Western Infirmary.

Exhibition of Museum Specimens in the Laboratory of the Zoology Department.

Demonstrations of rare books and other objects of interest in the Hunterian Library.

3 p.m. *Afternoon Session*

1. Dr. T. Stacey Wilson in a paper entitled *The Sphygmomanometer as a Means of Recording the Arm Pulse,* demonstrated how the sphygmomanometer could be modified to function as a plethysmograph and measure the volume of the pulse. With a large aneroid such as the Pachon oscillometer it was possible to measure the full arm pulse, while a small aneroid such as the Tycos recorded the pulsation in the main arteries only, and revealed variations in the arterial tone. Dr. Stacey Wilson showed records illustrating the method of estimating the cardiac efficiency and the arterial tone.

2. Dr. C. P. Symonds related three cases of *Otitic Hydrocephalus* with especial reference to the manometric readings, which in one case definitely excluded lateral sinus thrombosis as the cause. He emphasized the need of repeated drainage by lumbar puncture in certain cases in order to prevent secondary optic atrophy.

Dr. Micks asked whether a cerebral abscess was common in this condition.

Drs. Riddoch, Cohen, and McAlpine also discussed this paper.

Dr. Symonds replied.

3. Dr. Ivy Mackenzie described *The Projection of the Retinal Quadrants on the Lateral Geniculate Bodies and the Relation of the Quadrants to the Course of the Optic Radiations.* Circumscribed syphilis of both lateral geniculates was correlated with visual fields taken within 24 hours of death. Lower visual fields were related to mesial sides of geniculates, and upper to lateral. There was also evidence of oral and caudal projection of retinal quadrants on the geniculates.

4. Sir James Purves-Stewart described *Fractional Pneumo-radiography of the Brain.* He called attention to the value of fractional pneumo-radiography in cases of distortion or displacement of the cerebral ventricles by tumours, vascular lesions, scar tissue, &c. Complete filling of the ventricles is often unnecessary, whereas minimal quantities of air 10 cm. or less may be sufficient to demonstrate the upper limits of the ventricles and to indicate whether they are normal or abnormal in their position and outlines. He further emphasized the absence of discomfort to the patient as contrasted with the headache, vomiting, &c., which often supervenes after complete filling with air.

This communication was discussed by Drs. Hinds Howell, Nattrass, and Symonds.

5. Drs. John Parkinson, Clifford Hoyle, and William Evans (introduced) discussed *The Drug Treatment of Angina Pectoris.* The comparative value of sixteen drugs in the continuous treatment of angina pectoris (angina of effort) was determined in a series of 90 cases observed for 2½ years. None of the drugs tried proved to be sufficiently effective in reducing the number and severity of attacks to warrant its use in routine treatment. A measure of improvement, due to spontaneous variations or remissions, appeared to result from every drug and also from a placebo. Glyceryl trinitrate tablets proved to be by far the best means of relieving attacks, and equally effective for their immediate prevention. They can be used freely in this way without discomfort or risk. The tablets must be chewed to allow the drug to be absorbed from the mouth, as they are ineffective when absorbed from the stomach.

An interesting discussion followed this communication, and was taken part in by Drs. Herapath, Starling, Cowan, Claude Wilson, and Edgecombe.

6. Dr. W. T. Ritchie gave a communication on *Functional Auriculo-ventricular Dissociation with, and without Interference.* This form of dissociation is entirely distinct from that produced by complete *a–v* heart-block. The communication also dealt with Type I and Type II varieties of partial *a–v* heart-block.

7. Dr. Theodore Thompson described an *Aneurysm of the Aorta Treated by the Insertion of a Gold Wire.* The patient, a man of fifty, developed severe pain in the chest after receiving three heavy blows upon the upper part of the sternum. The Wassermann reaction in the blood was positive. An aneurysm of the aorta developed very rapidly and within three months formed a pulsating tumour which was adherent to and reddening the skin. Rest, restricted fluid diet and antisyphilitic treatment failed to arrest it. A wisp of gold wire was inserted into the aneurysm by Colt's method and within six months the aneurysm disappeared into the chest and the man returned to work and has been actively working in a tobacconist's shop for the past eighteen months.

Dr. Morley Fletcher referred to the original case treated by Sir Antony Bowlby and other cases.

Saturday Morning Session, 10 a.m.

1. Dr. D. McAlpine made *Some Observations on the Hypertensive Cerebral Attack.* The cerebral symptoms of arterial hypertension can be divided into two groups: (1) signs of cerebral oedema such as papilloedema and increased cerebrospinal fluid pressure are present; this form occurs chiefly under the age of forty and is characterized by severe headache; (2) signs of cerebral oedema absent—patient is usually over the age of forty; epileptiform attacks are common; the main precipitating cause seems to be an additional rise in blood-pressure. Venesection and vasodilators are advocated in treating both forms.

Drs. Feiling, Ellis, Sir William Wilcox, Drs. Tidy, and Parkes Weber discussed this communication.

Dr. McAlpine replied.

2. Dr. A. F. Hurst discussed *Peptic Oesophageal Ulcer and Recurrent Hiatus Hernia.* Peptic oesophageal ulcer produces characteristic symptoms and can be recognized by radiography, but as a special technique is required it is generally missed and the patient

regarded as neurotic. Recurrent hiatus hernia also gives rise to a characteristic syndrome, which calls for an X-ray examination in the horizontal position, without which radiological confirmation cannot be obtained.

Sir Charlton Briscoe had treated cases of oesophageal ulcer with alkalis with satisfactory results, and he did not consider that gastrotomy was necessary.

Dr. Speares referred to a case of oesophageal ulcer in which the only symptoms were dyspnoea and anaemia, and there were no gastric manifestations.

Dr. Parkinson referred to cases of angina which had been diagnosed as 'hiatus hernia' by German authorities.

3. Sir William Willcox described *Some New Points in the Treatment of Threatening Hepatic Necrosis in Toxic Jaundice.* Attention was called to the importance of early diagnosis; the early administration of glucose by mouth, subcutaneously, and if necessary intravenously; the full administration of alkalis by mouth; and the administration intramuscularly of calcium gluconate or 1 per cent. calcium chloride. In some recent cases, where cerebral symptoms had commenced, repeated lumbar puncture had been of great advantage.

4. Dr. J. Eason and Dr. R. Ogilvie (introduced) described *The Islets of Langerhans in Cases of Obesity.* The islets of Langerhans in 18 cases of obesity were compared with those in 15 lean subjects. Of the obese subjects 15 were found to possess (1) an abnormally high percentage area of islet tissue, (2) a normal number of islets per given area, and (3) islands the average size of which was definitely greater than the control.

This communication was discussed by Drs. N. Morris, George Graham, and Parkes Weber.

5. Dr. J. Craig described a *Basophil Adenoma of the Pituitary Gland.* The condition occurred in a woman of twenty-seven, who showed rapidly acquired obesity, amenorrhoea, vascular hypertension, large purple striae in the abdomen, pigmentation and ecchymoses of the legs, and marked decalcification of bones. The case was diagnosed during life, and at autopsy a small basophil adenoma of the pituitary gland was demonstrated.

Similar cases were mentioned by Drs. Abraham, Stanley Davidson, Parkes Weber, and Tidy. It was generally considered that some of these cases were due primarily to lesions of the suprarenals.

6. Dr. A. Glen (introduced) described *Changes in the Organs of Internal Secretion in Diabetes Mellitus.* Lantern slides were shown of sections of pancreas and anterior lobe of pituitary gland in seven cases of diabetes mellitus and one case of exophthalmic goitre. Apparent changes of a degenerative nature were demonstrated in the anterior lobe of the pituitary gland in sections from three young acute diabetic cases, and in one older diabetic in which there was congenital absence of one kidney.

7. Drs. G. Graham and E. R. Cullinan reported a *Case of Diabetes and Atheroma in a Young Adult.* A young man, aged twenty-seven, who had had diabetes for eight years developed a coronary thrombosis, and died of cardiac failure. The diabetes had never been severe, and the blood-sugar had been kept within normal limits by 20+18 units of insulin. The diet consisted of C. 60 gr., P. 70 gr., F. 125 gr. The aorta and all the arteries showed a nodular hyperplasia of the intima, with deep fat, rich in cholesterol and doubly refractive. The cholesterol in the arteries was increased, but less than in the arteries of a case of atheroma in an old man. The hypotheses for this change were discussed.

2 p.m. to 3 p.m.

Demonstration of Clinical Cases at the Western Infirmary.

Exhibition of Museum Specimens in the Laboratory of the Zoology Department.

3 p.m. *Afternoon Session*

1. Dr. C. P. Lapage discussed '*Allergy and the Exudative Diathesis in Childhood,* describing a type of child with intolerance to milk fats and to some vitamin preparations. The condition is often inherited, and the child through overloading of metabolism becomes liable to disturbance of the autonomic nervous system and to allergic manifestations.

2. Dr. Maurice Davidson discussed *Some Clinical and Radiological Problems Associated with Localised Inflammatory Reactions in the Lung.* He showed a series of X-rays illustrating the presence of transitory changes in the radiological appearances in various pathological conditions affecting the lungs. He pointed out some of the clinical and radiological difficulties in differential diagnosis, and discussed the pathogenesis of localized inflammations in the lung with special reference to the phenomena of allergy. He was of opinion that many of the difficulties in the diagnosis of such cases would be elucidated by the taking of serial radiograms at more frequent intervals than was usually done.

Dr. Chandler expressed the opinion that several of the cases mentioned were due to broncho-pneumonia.

Dr. E. W. Patterson also spoke.

3. Dr. R. Coope, in a paper entitled *The Frequent Failure to Make an Early Diagnosis of Pulmonary Tuberculosis* had analysed 103 cases of patients in whom for the first time phthisis had been discovered. Only five were really 'early'; 61 had cavities large or small, and in all, 86 out of 103 had advanced or moderately advanced lesions. He discussed possible causes of this frequent failure to make an early diagnosis.

4. Dr. J. B. Gaylor (introduced) reported *Investigations into the Innervation of the Lung—Some Clinical Inferences.* He gave a general description of the bronchial nerve supply. The vagal sensory nerve ending in the plain muscle of the bronchus was described and the possibility discussed of this being the site of origin of the Hering-Breuer reflex. Inferences were drawn from the general morphology of bronchial musculature to offer explanations as to the causes of the physical signs in asthma.

5. Dr. B. Schlesinger discussed *The Significance of the Rheumatic Nodule.* In a review of 1000 cases of rheumatism in childhood with carditis, 70 were found to have nodules. This proportion was thought to be low on account of the number of convalescent cases in the series. In one case the nodules appeared more than a year prior to any demonstrable cardiac disease, and in four little or no involvement of the heart was ever detected. The close association of chorea was noted in several instances. Nodules might either have an insidious afebrile onset or might follow an acute pyrexial cardiac relapse. In this event an appreciable interval usually occurred, up to eight to ten weeks, before the nodules made their appearance with the fresh rheumatic activity. Nodules were always associated with a high erythrocyte sedimentation rate. If this persisted the case showed no likelihood of early recovery and in fact generally progressed downhill. On the other hand, a falling sedimentation rate was a favourable omen and usually indicated that the nodules would soon disappear. Cases in which nodules appeared within a short interval after a cardiac relapse were serious and often proved fatal. Owing to the severe and generalized rheumatism with which nodules were usually associated, it was not surprising that the ultimate prognosis was often bad, but that was no reason for regarding all cases with the proverbial pessimism.

This communication was discussed by Drs. Nixon, G. B. Fleming, and Tidy.